Neurology

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THE AMERICAN ACADEMY OF NEUROLOGY

SEPTEMBER--1955
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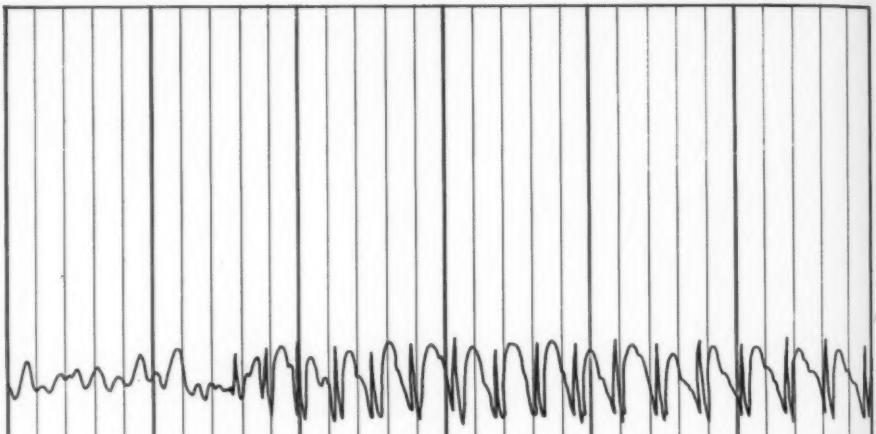

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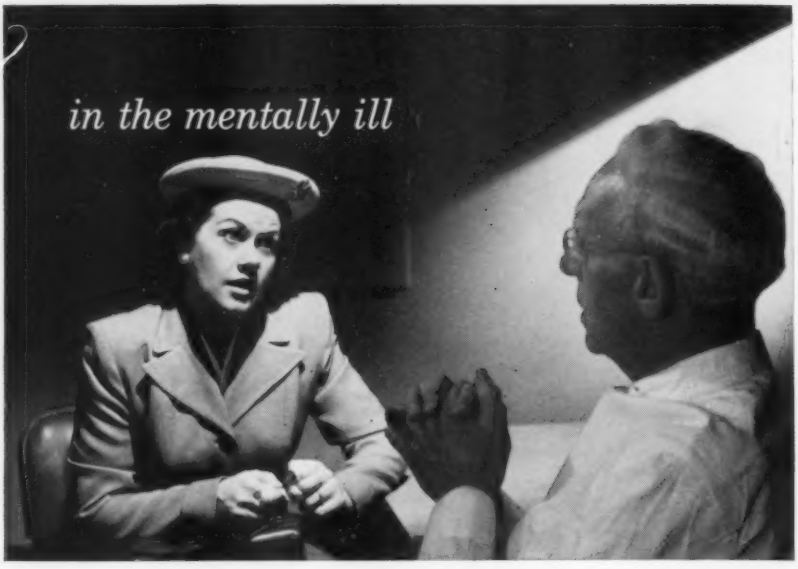

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INFORMATION FOR *Authors*

NEUROLOGY, the official publication of the American Academy of Neurology, has been instituted to provide a medium for prompt publication of articles dealing with neurology and its cognate fields and to stimulate individual investigation in these various fields.

Manuscripts of papers read at meetings of the Academy must be filed with the secretary at the time of the meeting, and will be published if acceptable to the editorial board. They are the property of the Academy, and authors who wish to publish them elsewhere must first request release.

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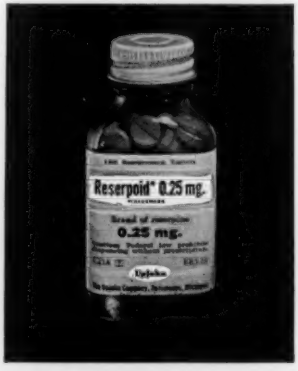

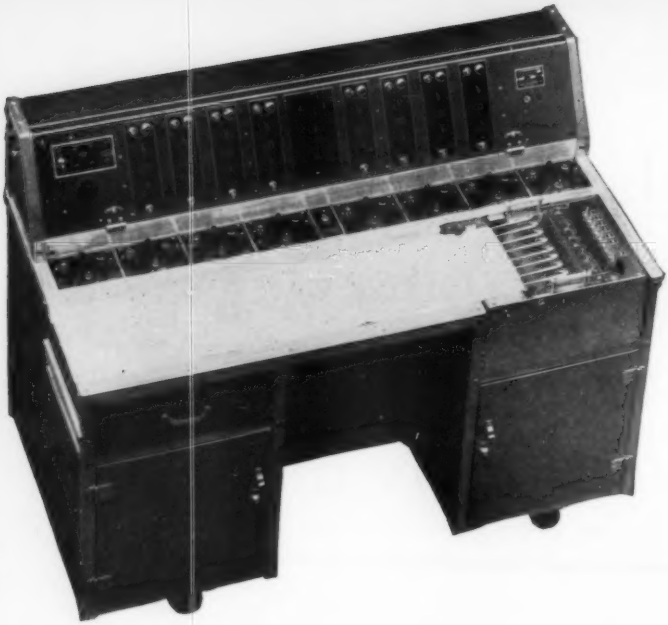

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---

1. Greenstein, L., and Sapirstein, M. R.: A. M. A. Arch. Neurol. & Psychiat. *70*:469 (Oct.) 1953. • 2. Smith, B., and Forster, F. M.: Neurology *4*:137 (Feb.) 1954. • 3. Smith, B. H., and McNaughton, F. L.: Canad. M. A. J. *68*:464 (May) 1953. • 4. Whitty, C. W. M.: Brit. M. J. *2*:540 (Sept. 5) 1953. • 5. Doyle, P. J., and Livingston, S.: J. Pediat. *43*:413 (Oct.) 1953. • 6. Timberlake, W. H., Abbott, J. A., and Schwab, R. S.: New England J. Med. *252*:304 (Feb. 24) 1955.

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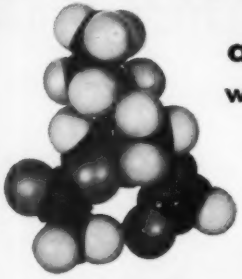

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1. Selling, L. S.: J.A.M.A. **157**: 1594, 1955.
2. Borrus, J. C.: J.A.M.A. **157**: 1596, 1955.

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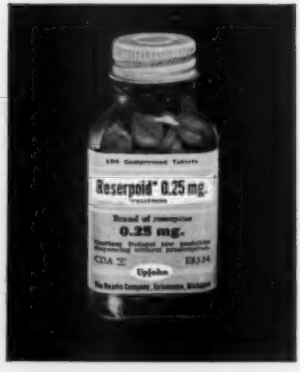

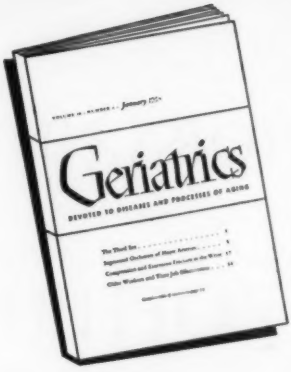

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Volume 5 Neurology Number 9

The Dimensions of Neurology

Howard D. Fabing, M.D.

THE PRACTICING NEUROLOGIST finds himself busily engaged on many medical fronts today. The big reason for his sizeable place in the present-day medical family is that he is now a therapist—he helps sick people get well. His dimensions as a diagnostician are somewhat greater than those of his grandfather and his father in neurology because he is armed with new radiologic, electrophysiologic, and chemical tools, but it is his new pharmacopeia that has made for the real enlargement of his effective dimensions. The arsenicals, phenobarbital, nux vomica, and potassium iodide were just about all there was to the therapeutic aids available 25 years ago. The remarkable parade of new drugs in the treatment of combined system disease, convulsive disorders, migraine, narcolepsy, myasthenia gravis, neurosyphilis, meningitides, mood disorders, and all the rest has changed the whole scope and aspect of neurology in the last quarter century.

What of the future? Will these dimensions grow, and along what lines? There is much of neuroanatomy and neuropathology to be studied, and we may expect these fields to advance with the help of new tools, many of them borrowed from the busy field of neurophysiology. But isn't it more likely to expect the biggest strides to be made in neurochemistry and neuropharmacology, as in the immediate past?

Over the past few years certain piperidyl compounds have been tested as possible therapeutic agents in neurology.[1] During the past year one of them, alpha-(4-piperidyl) benzhydrol hydrochloride, has been found to exhibit definite, though inconsistent, therapeutic effects in schizophrenic dissociation syndromes.[2] Heath and his associates[3] and Himwich[4] have also begun to study this

Presidential address read before the seventh annual meeting of the American Academy of Neurology, Houston, Texas, April 28, 1955.

compound as a therapeutic agent. Our results were significant enough to encourage an inquiry into the ability of this compound to affect experimental psychoses induced by hallucinogenic drugs.

In November 1954, it was demonstrated that this piperidyl compound (Frenquel) blocked the development of LSD-25 psychosis when given to normal subjects as a premedication.[5] It was also found that an LSD-25 psychosis could be brought to an abrupt end at the height of its development by the intravenous administration of Frenquel.[6] Later it was discovered that mescaline psychosis could be blocked by the same drug when it was given as a premedication, and could be aborted by the intravenous administration of the drug as well.[7]

In February 1955, we stumbled upon another finding when a physician undergoing a prostatectomy developed a confused state on the second postoperative day. Not only his words, but the manner in which they were spoken, had a familiar ring as he described his condition. He told of sensations of levitation, of visual and haptic hallucinations, of a feeling of drifting into a weird world dissociated from the real one, and of his sensation of fear and foreboding which accompanied it. We have all seen many patients with postoperative confusion, but this was the first one the author had ever looked at intensively. The similarity between his stream of talk and that of the LSD-25 and mescaline subjects was striking. Then he was given 50 mg. of Frenquel intravenously and urged to go on talking. He described the progressive amelioration of his dissociated mental state during the next half hour. The medication was continued orally for the remainder of his hospital stay, and his course was uneventful thereafter. This clinical experience has launched us on an inquiry into postoperative confusional syndromes, and we hope to be able to report our results[8] in the near future.

These therapeutic adventures have led me to inquire into what is a new field of neurochemistry for me. I should like to share some of this with you because I find it interesting, and because I think it is indicative of the expanding dimensions of neurology.

Drugs which contain an intoxicating principle were described[9] by the Chinese in the fifteenth century before Christ. The Germans[10] came to call them the "phantastica." More recently[11] they have been labelled "hallucinogens." The list is not a long one. A look at the major phantastica of vegetable origin reveals that an indole nucleus is common to their chemistry. They include lysergic acid diethylamide (LSD-25) from rye rust, yohimbine from the bark of the

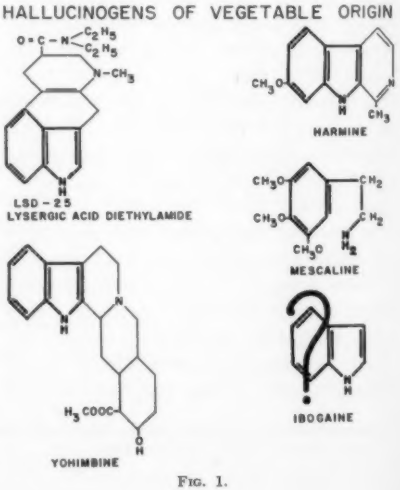


FIG. 1.

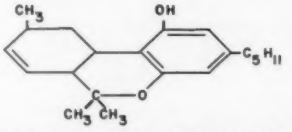
yohimbehoa tree, harmine from the Turkish plant, *peganum harmala,* and ibogaine from a bean grown by the Ibo tribe of Central Africa. Mescaline, from the mescal or peyotl cactus of Aztec origin, is a potential indole as well (figure 1). A remarkable Siberian hallucinogen from a fungus (*amanita pantherina*) which grows on the larch tree has not been studied chemically.

The one exception to this rule about the indolic structure of hallucinogens is the oil from the flowering tops of the female hemp plant, cannabis, or marihuana, or bhang, or charas, or ganja, or hashish as it is called, depending on where you live on this earth. This compound contains no nitrogen, but is a dibenzopyran, as is pyrahexyl,[12] an approximate compound with similar properties, synthesized by Roger Adams[13] some 15 years ago (figure 2).

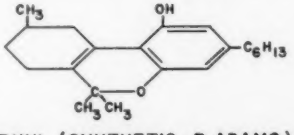
There are a few hallucinogens of animal origin as well. In 1936 Nieuwenhuysen[14] found that tryptamine produced negativism and catalepsy in cats. Recently Evarts[15] has shown that bufotenine, an extract of the skin of toads and lizards, produces ataxia, motor disturbance, indifference to tactile stimuli, and what might be summed up as schizophrenic behavior in the monkey. "Pink adrenaline," or adrenochrome, produced a harrowing temporary psychosis in Osmond[16] when he injected it intravenously into himself and other volunteers last year. Although it has been difficult to repeat this observation, the single report is significant. A look at their chemical structure reveals that these substances are all indoles. Porphobilinogen is included in this list of hallucinogens of animal origin. Watson,[17] long a student of the porphyrins, has concluded that this compound or one of its immediate derivatives is the causative agent of the acute intermittent form of porphyria. Although porphobilinogen is not an indole,[18] inspection of its structural formula reveals that the two short carbon chains which extend upward from the pyrrol ring are spatially about as large as a benzene ring, and that with the closure of these chains into such a ring, an indole would emerge (figure 3).

We may summarize the foregoing by saying that the known hallucinogens which produce a schizophrenic or pseu-

THE CANNABIS HALLUCINOGENS



TETRAHYDROCANNABINOL (FROM HEMP)



PYRAHEXYL (SYNTHETIC - R. ADAMS)

FIG. 2.

HALLUCINOGENS OF ANIMAL ORIGIN

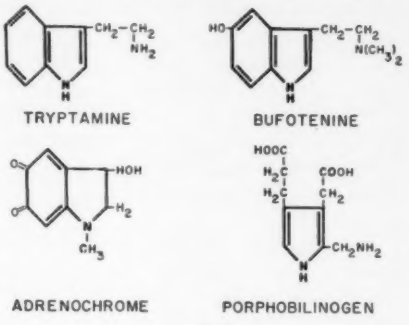


FIG. 3.

doschizophrenic state in man and in experimental animals are indoles or potential indoles, if we except cannabis. All of them act in minute quantities, varying from 0.1 mg. in the case of LSD-25[19] to 400 mg. in the case of mescaline[20] in man, which provokes the thought that they probably exert their effects on enzyme systems concerned in brain metabolism.

The possibility of the relationship of these indoles to clinical schizophrenic syndromes weaves itself throughout these data. We have all spent many an hour speculating about the etiology of schizophrenia,[21] and Bleuler[22] spent a lifetime at it. He concluded (regretfully, I think) that the disease was psychogenic. Can the conclusion of this devoted student of the cause of one of the most cruel diseases which beset mankind be refuted? I do not think so with the data now in hand, but it is possible to make the beginnings of a case for an alternate etiologic possibility, that of metabolic error. Four possibilities exist.

Possible metabolic error number one concerns itself with tryptamine formation. Erspamer[23] states that the normal metabolism of tryptophan, an amino acid set free from protein by tryptic digestion, is its conversion to 5-hydroxytryptophan by oxidation, then to serotonin by decarboxylation, then to 5-hydroxyindoleacetic acid by oxidative deaminization, and ultimately to catabolism. A metabolic error is possible in the very first step of this process (figure 4). If tryptophan is decarboxylated before its 5-hydroxy-derivative is formed, tryptamine results.[24] As noted above, Nieuwenhuysen[25] found that this indolethylamine produces catalepsy and negativism in cats, and that this state persists for several days after intravenous injection of 100 to 150 mg. of the compound. More than 30 years ago Sullivan[26] made an observation in the human which fits in nicely here. He isolated tryptamine from the urine of patients suffering from pellagra, a disease which can produce schizophrenic symptoms. This opens up an attractive possibility which deserves further study.

Possible metabolic error number two has received a good deal of attention lately. It concerns the fate of serotonin, the neurohumoral agent which has been

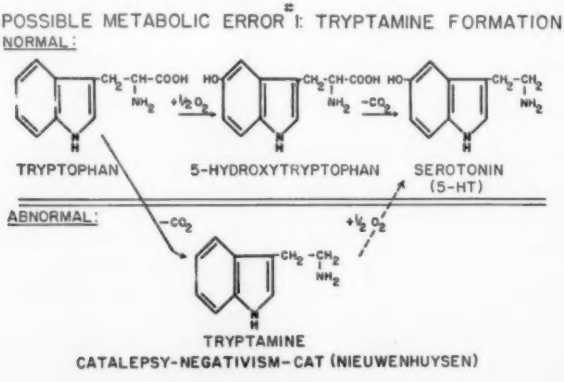


FIG. 4.

found to be a normal constituent of brain tissue. It is possible to speculate that it may not deaminize to 5-hydroxy-indoleacetic acid in the normal way, but may methylate instead, as in the skin of amphibians and in certain fungi[27] (figure 5). In such a scheme it becomes n-methylserotonin in the first methylation, and n-dimethylserotonin, or bufotenine, in the second. This is the indole which Evarts[28] has found to cause a "schizophrenia" which lasts for several hours when it is injected in the monkey in doses of 3 mg./kg.

Is bufotenine hallucinogenic for humans as well as for monkeys? The aboriginal men of Hispaniola and South America have carried out this experiment for us. Fra Ramon Pane, who came to America with Columbus on his second voyage, in 1496 described the ceremonial use of cohoba,[29] a snuff derived from the seeds of the *piptadenia peregrina* tree, reporting that "it intoxicates them to such an extent that when they are under its influence they know not what they do." This inhalant was so potent in producing temporary dissociation states that it became tribal custom for the women to tie up the Otomaco Indians when they used it. Last year Stromberg[30] determined that bufotenine was the active indolic principle of cohoba.

Gaddum[31] has found that LSD-25 is a potent antagonist of the constrictor action of serotonin, and stated: "It is possible that the serotonin in our brains plays an essential part in keeping us sane and that this effect of LSD-25 (the production of temporary madness) is due to its inhibitory action on the serotonin in the brain."[32] Woolley and Shaw,[33] on the other hand, bring forth evidence that psychoses may be caused by too much serotonin in the brain. We may expect to hear much more about all this as investigation of serotonin and its derivatives goes forward.

Possible metabolic error number three concerns the biochemical lesion which may arise from an error in epinephrine chemistry. The similarity between the structural formula of mescaline and this important endocrine has made many people suspect that the key to the riddle

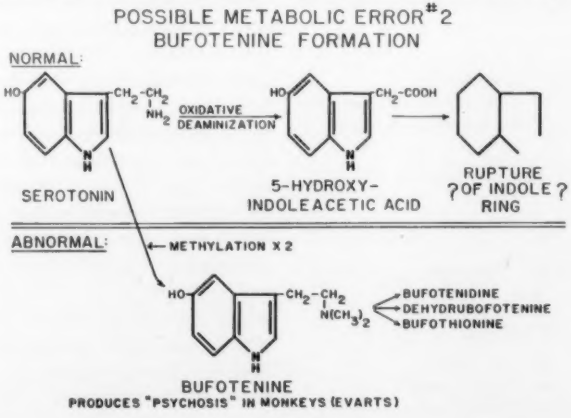


FIG. 5.

of schizophrenia may be found in an error of its metabolism (figure 6). When adrenaline stands in a bottle for a long time it turns pink. This pink color is due to its oxidation or partial oxidation to adrenochrome, an indole which is difficult to isolate. In 1954 Hoffer, Osmond, and Smythies[34] reported that the intravenous injection of 1 to 10 mg. of adrenochrome (synthesized by Hutcheon) in self-experiments and in volunteers produced schizophrenic dissociations of as long as four days' duration. Their protocols are worthy of study. Another adrenaline oxidation product is adrenoxin. It has been postulated[35] that this substance may also be of etiologic importance in the production of schizophrenic psychoses. The possibility of metabolic error in epinephrine chemistry deserves serious consideration in the search for a chemical cause for schizophrenia.

Possible metabolic error number four is a tenuous one, and probably does not deserve the attention due the other three. It is prompted by our study of postoperative confusional states which is under way. This reaction seems to occur most often after two surgical procedures: prostatectomy and the pinning of broken hips. What is the common denominator in these operations? They are performed on old people for the most part, but the factors of arteriosclerosis, hypertension, and nitrogen retention are not important. The type of anesthesia used does not seem to be significant. It is the rule rather than the exception that a lag period of 24 to 36 hours elapses after operation before dissociation symptoms occur, and, therefore, the immediate connection of the psychotic state and the surgical trauma is not apparent. It has occurred to the author that urine and bone marrow both contain porphyrins and perhaps their precursors.[36] In these instances raw tissue may be said to come into direct contact with these chromogens, and perhaps they are altered or their absorption is hastened in the wound area. This highly speculative thought is brought forward to explain schizophrenia-like postoperative confusions. Acute intermittent porphyria may produce a schizophrenic picture clinically. Porphobilinogen is not an indole, but is chemically akin to the indoles. Its immediate derivatives are unknown,[37] but it is not beyond conjecture that they may be of indolic structure (figure 7). Could it be possible that schizophrenia might result from a metabolic error in this system? Perhaps it is worth thinking about, even though there is little evidence to support this concept.

The clinician has always wondered whether schizophrenia was a disease entity or a reaction pattern due to many causes. Four speculative possibilities have been presented concerning the types of metabolic error which might

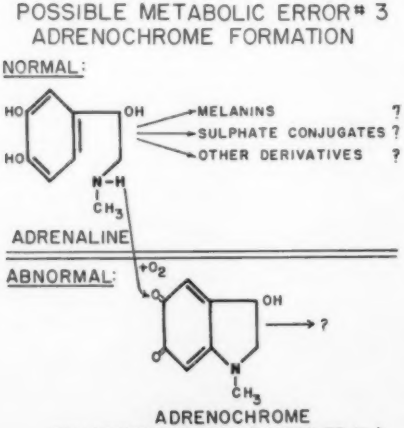
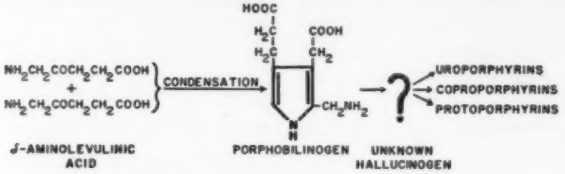


FIG. 6.

POSSIBLE METABOLIC ERROR*4
FORMATION OF ABNORMAL PORPHYRIN PRECURSORS



"THE BELIEF THAT PORPHOBILINOGEN OR A CLOSELY RELATED COMPOUND, PERHAPS AN IMMEDIATE DERIVATIVE, IS FUNDAMENTALLY RELATED TO THE ABDOMINAL AND NERVOUS SYMPTOMS OF THE ACUTE DISEASE (PORPHYRIA) SEEMS JUSTIFIED." (CECIL WATSON, ADV. INT. MED, 6: 277, 1954.)

FIG. 7.

be implicated in the production of these clinical disorders. Perhaps all four of them may be operative; on the other hand, none of them may be of etiologic importance. The new pharmacologic agents which are demonstrating some therapeutic value in these patients—reserpine, chlorpromazine, and Frenquel—are all inconsistent in their efficacy. They seem to produce tangible results in no more than 60 per cent of cases in the series reported[38] to date. These drugs, which the author has called *ataraxics*[39] (after the word *ataraxy* of Greek origin, meaning *freedom from confusion* or *peace of mind*), are all different in chemical structure (figure 8).

No investigator has come forward with a clear explanation of the mode of action of any of these drugs, although recent studies by Mayer-Gross and associates[40] and by Hoff and Arnold[41] permit us to speculate that they might inhibit the effects of hallucinogens (LSD-25 specifically) on phosphorylation or on the citric acid cycle in glucose metabolism. Could it be that they correct a portion of the metabolic errors which may produce the schizophrenic reaction pattern, but not all of them? I leave you with this question along with many others. I find at least two questions that are urgent. First, why doesn't somebody try to devise a diagnostic laboratory test for schizophrenia which seeks out the indoles which may be present in a peculiar way in the blood or urine of these patients? Second, why can't some new tools be devised to screen potential new ataractic drugs? If they must be tested only in the human, their discovery will

THE ATARAXICS

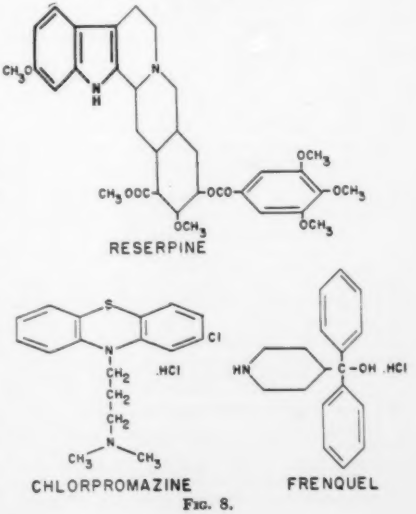


FIG. 8.

be slow and laborious.

We may be assured that a great deal of work will be done in this field in the days just ahead, and we may find a real ray of hope for a large and wretched group of sick people in this type of investigation. The chemists and the pharmacologists will do the most of it, but they will need the sober advice and the guiding hand of the clinician along every step of the way. By temperament and training neurologists are best able to provide this help – the kind of help provided to the other neurochemical and neuropharmacologic researches which are bearing so much good fruit for our chosen field of medicine these days. It seems to me, as it does to Sir Francis Walshe,[42] that, as these chemical and pharmacologic doors are opened, the dimensions of neurology are large indeed.

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■ I pass now to another and capital question, the solution of which will explain a great many mysterious pathological cases observed in man: How is it that sensibility is not lost and is only more or less diminished, although the spinal cord is deeply altered? This question seems to be solved by the following experiments: If we divide transversely the posterior columns in the upper part of the lumbar region in a mammal, we find that there is hyperaesthesia everywhere behind the section; if we then divide the posterior parts of the lateral columns and the posterior gray horns, we find that the hyperaesthesia increases also everywhere behind the section. If the section is carried farther, so that the whole posterior half be divided transversely, the posterior part of the gray matter, behind the central canal, being cut, the hyperaesthesia remains excessive everywhere behind the section. When another section is made, cutting a little more of the central gray matter, the hyperaesthesia disappears from everywhere at once, and a certain degree of anesthesia appears also everywhere behind the section. At last, if the whole of the central gray matter be divided, with also a good part of the basis of the anterior horns, sensibility is very much diminished everywhere behind the division, and it disappears entirely everywhere at the same time when the section has left only the anterior ports of the anterior columns. The general result of this experiment is, that any change that takes place in the state of sensibility—either an increase or a diminution—shows itself everywhere, at the same time, behind the section.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Prostigmine-Responsiveness and the Diagnosis of Myasthenia Gravis

Lewis P. Rowland, M.D.

ALTHOUGH THE CLINICAL FEATURES of myasthenia gravis were delineated before 1900,[1,2] it has been the experience of several clinics that the number of patients with this disorder has increased in the past two decades. This apparent increase is probably due to the interest stimulated by the efficacy of prostigmine in treatment[3] and diagnosis.[4]

Some early reports suggested that patients with other neuromuscular disorders might improve after the administration of prostigmine,[5,6] but most observers stated that only in myasthenia would the improvement be unequivocal and diagnostic.[7,8,9] Responsiveness to prostigmine became an important criterion in making the diagnosis. If the weakness is not corrected by prostigmine, some authorities would be reluctant to classify a syndrome as myasthenia gravis except when the symptoms are very mild, weakness is confined to extraocular muscle, or in the terminal phase of the diseases.[10]

It is the purpose of the present report to describe a small series of cases which illustrate the necessity to reconsider this concept, and to demonstrate some of the problems of clinical definition which may arise.

A SYNDROME CLINICALLY INDISTINGUISHABLE FROM MYASTHENIA GRAVIS, BUT LACKING RESPONSE TO PROSTIGMINE

Walsh [11] has described patients whose clinical symptoms and signs were those of myasthenia gravis, but who did not respond to prostigmine. His cases were not examined anatomically and the possibility that some other disease may have been present cannot be excluded, even though it seemed unlikely. The following case, previously reported[12] but not presented in detail, demonstrates that autopsy examination of such patients may fail to disclose any abnormality of muscle, nerve, or central nervous system.

Case 1.—A 45 year old woman noted the onset of diplopia after an upper respiratory infection in February 1951. One year later her voice assumed a nasal quality and shortly thereafter dysphagia was noted. She lost 50 pounds during the next few months. Weakness of the extremities ensued and she was admitted to the Neurological Institute of New York on August 17, 1952.

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General examination was normal. There was slight weakness of the extremities but no atrophy. Tendon reflexes and sensation were normal. The cranial nerves were normal except for weakness of the medial and lateral recti bilaterally and dysarthria.

Normal values were obtained for the following laboratory tests: blood count; urinalysis; blood nonprotein nitrogen, sugar, carbon dioxide, and chloride; cerebrospinal fluid; roentgenograms of the chest and skull; electromyography; and radio-iodine uptake.

The administration of 1.5 mg. prostigmine intramuscularly on two occasions resulted in equivocal improvement of voice and of swallowing, but made the diplopia worse and induced fasciculation of skeletal muscle. She also felt worse following the intravenous injection of 10 mg. of Tensilon and developed generalized fasciculations, but there was no change in her symptoms. Oral prostigmine, in doses up to 30 mg. four times daily and supplemented by ephedrine, produced no improvement when given for one week. During the second week of a later trial of oral prostigmine, she had more severe dysarthria and dysphagia. Respiratory difficulty appeared and was not relieved by the administration of 1.5 mg. prostigmine parenterally. Medication was discontinued and she was placed in a mechanical respirator on September 14. Improvement was rapid and she was able to breathe without assistance after five days. On September 30, 1952 she was discharged without medication.

At home she experienced transient episodes of dyspnea and was readmitted on October 12, 1952.

Vital signs were again normal. Her color was ashen, but not cyanotic. She was restless and the accessory muscles of respiration were being used. General examination was normal and there was no weakness of the extremities. There were no fasciculations or muscle atrophy. The deep reflexes were normal. The cranial nerves functioned normally except that the uvula was immobile and the tongue protruded weakly. Ocular movements at this time were grossly normal, but she complained of diplopia.

During the night she began to have myoclonic movements of the shoulders and upper extremities. Respiration became irregular and rapid, and she lapsed into coma. Oxygenation was maintained by positive pressure and although her color improved she remained unresponsive. The movements of the upper extremities recurred and were followed by atonia and apnea. This sequence of events was repeated several times, and was not affected by 200 mg. phenobarbital or 2 mg. prostigmine administered intramuscularly. An endotracheal tube was inserted and she was placed in a mechanical respirator. She gradually improved and regained consciousness several hours later.

A tracheotomy was performed the next day, and on October 22 she was started on octamethyl pyrophosphoramid (OMPA) 5 mg. twice daily. This was gradually increased to 12 mg. twice daily on October 27. There was no improvement and the drug was discontinued on November 1 because of diarrhea and fasciculation.

For the next few weeks she remained in the respirator almost continuously and she was fed by means of a nasogastric tube. She was then able to remain out of the respirator for several hours each day and after December 15 was able to breathe without assistance most of the time.

During this period she was again given prostigmine, starting with minute doses which had no effect at all and gradually increasing until she received 0.75 mg. in a single parenteral dose. This amount was followed by increased diplopia and fasciculation. It was felt that the diplopia might have been aggravated because of partial and unequal improvement of the muscles involved, but the general reaction caused so much distress that further testing with larger doses was not attempted. An intravenous injection of 2.5 mg. of Tensilon aggravated the diplopia but had no other effect; 5.0 mg. Tensilon also aggravated the diplopia and may possibly have increased the range of ocular movements but did not affect respiration; after receiving 10.0 mg. she developed fasciculation and ptosis of the eyelids.

For one week an unsuccessful attempt was made to wean her from the respirator by using a rocking bed. On February 3, 1953 she suddenly became unconscious and had to be returned to the respirator. She improved rapidly and during the next two days she was able to remain out of the respirator for a few hours at a time. However, on February 6 while on the rocking bed, she suddenly became apneic and could not be revived.

Postmortem examination: There was bilateral lobular pneumonia and acute bronchitis, but

examination of the central nervous system revealed no abnormality and the peripheral nerves of the brachial plexus, one sciatic nerve, and both femoral nerves were all normal. The rectus, temporal, diaphragmatic, and psoas muscles were all normal. In the pectoralis major there were scattered muscle fibers which showed hyaline degeneration, with an increase in the number of muscle and sarcolemma nuclei. Some other fibers were narrow but not degenerated and there were no inflammatory changes. These findings were thought to be of doubtful significance. The thymus was not recognized grossly, but random sections of the anterior mediastinal fat revealed a few microscopic remnants of thymic tissue. The thyroid showed a single small focus of lymphocytic infiltration and there was a microscopic cortical adenoma of the left adrenal. The heart, kidneys, and pituitary were normal. There was acute congestion of the liver.

Comment: This syndrome included symptoms of ocular, pharyngeal, palatal, and respiratory muscle weakness. Variability in the intensity of symptoms was documented by the fact that she survived two separate exacerbations requiring treatment in a mechanical respirator and subsequently died while on a rocking bed. Although there may have been some effect on ocular muscles, the repeated test doses of prostigmine and Tensilon failed to produce improvement of a degree sufficient to be considered as of diagnostic significance. Therapeutic trials of oral medication with prostigmine and OMPA also failed, and the administration of curare or quinine was avoided because of her precarious situation. At autopsy there were no significant histologic changes other than pneumonitis. Whether she actually had myasthenia gravis is a matter of definition, but before the introduction of prostigmine her disorder would certainly have been so classified. Indeed, she fits perfectly the subtitle of Oppenheim's monograph on myasthenia, "Bulbar paralysis without anatomical findings." [1]

A similar, but less conclusive problem of this nature has been encountered more recently.

Case 2.—A girl was born in the Presbyterian Hospital of New York on January 28, 1954. Her mother was known to have had myasthenia gravis for three years and experienced a slight exacerbation of symptoms prior to term. The delivery itself was uneventful, but the baby's cry was weak, her face was expressionless, there was no resistance to attempts to open the eyes, the pharyngeal reflexes were absent, and she had difficulty in sucking. Nasogastric alimentation was necessary (figure 1). The extremities moved normally and tendon reflexes were intact. Ocular movements were normal.

In response to repeated test doses of prostigmine in amounts up to 0.5 mg. subcutaneously, there was equivocal improvement in the vigor of her cry, but there was never any improvement in her ability to suck or in her facial appearance. Despite the lack of definite response prostigmine was continued, 0.2 mg. every four hours subcutaneously, and no adverse effects were noted. When the baby was one week old it

FIG. 1. *Case 2.* Photograph taken a few days after birth to illustrate nasogastric tube for alimentation, open mouth, and lack of facial animation in a girl with presumptive neonatal myasthenia gravis.

was thought that she had improved somewhat; oral feeding was started and prostigmine was discontinued. Although she maintained her improved status for a few days, she soon began to take less milk by mouth and vomited several times. The facial immobility and weak cry were unchanged. She developed physical and roentgenographic evidence of pneumonitis and had fever (101° F.). She was treated with antibiotics; prostigmine and nasogastric tube-feeding were resumed. Again there was no distinct response to prostigmine, but she improved during the next few days. She was then able to suck adequately and her cry became louder although her face still lacked animation. The improvement was maintained when prostigmine was stopped and she was discharged without medication on March 2, 1954. She has developed normally since then and when last seen at the age of 16 months she showed no abnormality.

Comment: This child born of a myasthenic mother had symptoms for about eight weeks after birth. The transient nature and the character of her symptoms were similar to those previously reported to be characteristic of neonatal myasthenia.[13] Unlike most of the other children with the syndrome, however, this baby never showed a definite response to prostigmine. It is therefore of interest that the child reported by Gans and Forsdick[14] also responded poorly to prostigmine. The use of curare or quinine is inapplicable in these infants and in the absence of a diagnostic pharmacologic test there may remain some doubt, but it was the opinion of those in attendance that this girl did suffer a myasthenic syndrome.

MYASTHENIA GRAVIS WITH TEMPORARY LACK OF RESPONSE TO PROSTIGMINE

It has been recognized that the effect of prostigmine in myasthenia gravis varies from patient to patient and from time to time in the same patient. This variability may create some confusion if the response to prostigmine is minimal or absent at the time diagnostic studies are performed. There are some patients who fail to respond to prostigmine initially, but who later behave in a more typical fashion.

Case 3.—A 43 year old woman was well until 1950, when she rather abruptly began to have difficulty in keeping her eyes open. Difficulty in chewing and swallowing appeared one month later and diplopia followed. She was referred to a neurologist who thought that she had myasthenia gravis and administered test doses of prostigmine (1.5 mg. intramuscularly) on several occasions, but she failed to improve. She therefore received no specific therapy and her symptoms became worse during the next six months. She was then admitted to a nearby hospital and cortisone was administered for one week without effect. When the cortisone was discontinued she again received a test dose of prostigmine and this time she improved dramatically. She was then started on oral prostigmine, 150 mg. daily, and improved significantly for the next three months. Her symptoms then recurred and she became incapacitated despite treatment with prostigmine in amounts up to 300 mg. daily, tetra-ethyl pyrophosphate and OMPA in varying amounts, and ACTH. Diplopia and ptosis were prominent. Dysarthria was constant and dysphagia was occasionally severe enough to require tube-feeding. She stayed in bed most of the time and occasionally had brief episodes of dyspnea.

When she was seen at the Clinical Center of the National Institutes of Health in 1953, there was pronounced weakness of the extremities and of the muscles innervated by cranial nerves, but there was no atrophy or reflex abnormality. The administration of prostigmine in amounts up to 10.5 mg. in 60 minutes intravenously or 900 mg. per day orally failed to produce significant improvement and may actually have precipitated additional weakness.[15]

Later she suffered an exacerbation of symptoms and had to be treated in a mechanical respirator. At first she was able to gesture, grimace, and communicate by writing, but when medication was completely discontinued she became virtually immobile. When prostigmine was restarted five days later (1.0 mg. per hour intramuscularly), she regained her limited abilities.

Comment: It is possible that the original test dose of 1.5 mg. prostigmine was inadequate and that larger amounts might have produced the expected results. It is of interest, however, that the usual amount proved to be adequate several months after the initial trials. The subsequent course and response to prostigmine-withdrawal indicate that what may seem to be complete refractoriness to prostigmine may be merely relative.

One other patient has been seen whose course suggests a delayed response to prostigmine, but whose clinical picture is confusing and difficult to classify.

Case 4.—A 43 year old woman was admitted to the Clinical Center of the National Institutes of Health in 1954. Twenty years previously she began to have intermittent weakness of the legs, resulting in frequent falls. In 1935 she noted weakness of the arms and fingers, difficulty in chewing, dysphagia, diplopia, ptosis, and dysarthria. There were minor fluctuations in the severity of these symptoms, but they persisted. In 1939 the diagnosis of myasthenia gravis was suggested by her personal physician, but she did not respond to a test dose of prostigmine. In 1940 she was first admitted to the Hospital of the University of Pennsylvania. Prostigmine and quinine tests failed to confirm the diagnosis and the electromyographic response to ulnar stimulation was not typical (see below). She was treated with desoxycorticosterone without success. In 1942 she was readmitted and her response to quinine suggested the diagnosis of myasthenia, as did her electromyogram, but her response to prostigmine was poor. In 1947 she was admitted for the third time, and again the electromyogram was atypical. She was discharged on oral prostigmine medication, but her condition did not change much. In 1950 she was readmitted because of diarrhea and dermatitis. Roentgenographic examination of the gastrointestinal tract was normal and a biopsy of skin showed only chronic fibrosis and hyperpigmentation. During the course of this admission she improved markedly in response to prostigmine and she maintained this improvement on 22.5 mg. orally every two and a half hours during the day and 45 mg. at bedtime. Her condition remained unchanged thereafter except that in 1952 she began to have occasional attacks of pain, swelling, heat, and redness of various joints, most frequently the wrists.

General physical examination in 1954 revealed no abnormality except for macular cutaneous lesions (figure 2). There were no abnormalities of the joints. The cranial nerves were normal except for weakness of the orbicularis oculi and some weakness of the orbicularis oris. Her strength was difficult to evaluate; she could move all muscles through a full range of motion against gravity, but she did not sustain any position for more than a few seconds without fatigue and she could not sustain any motion against resistance. There was no atrophy, fasciculation, or myotonia. Tendon reflexes and sensation were normal.

Urinalysis, phenolsulfonphthalein excretion, hemogram, erythrocyte sedimentation rate, serological test for syphilis, basal metabolism, radioiodine uptake, serum precipitable iodine, blood urea nitrogen, sugar, cholesterol, sodium, potassium, calcium, phosphorus, albumin, globulin, alkaline phosphatase, cephalin floccula-

FIG. 2. *Case 4.* Myasthenia gravis with several atypical features. The skin lesions were thought to be due to dermatitis factitia. A skin biopsy showed chronic fibrosis and hyperpigmentation.

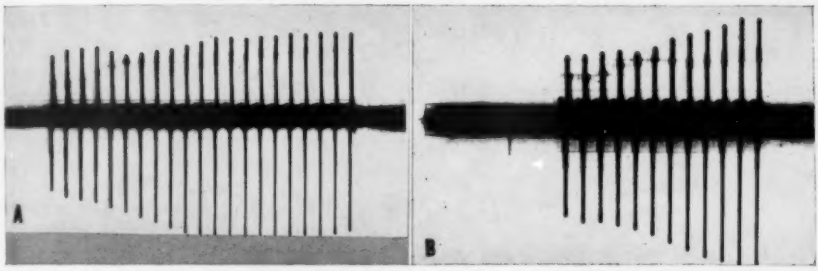

FIG. 3. *Case 4.* Electromyographic response of the abductory digiti quinti to stimulation of the ulnar nerve at the elbow according to the technic of Harvey and Masland.[41] *A.* The record obtained two hours after her last regular dose of prostigmine. Instead of the decline in height of the action potential usually observed in patients with myasthenia gravis, there is an increase (the first potential measures 7.25 mV., the tenth, 10.25 mV.). *B.* Record obtained 10 minutes after the administration of 0.5 mg. prostigmine intravenously (first potential, 7.25 mV.; tenth, 11 mV.). The same kind of record had been obtained at the University of Pennsylvania 14 years earlier (1940).

tion, thymol turbidity, bromsulfalein excretion, and bilirubin were all normal. The electrocardiogram was normal and roentgenograms of the lungs, mediastinum, gastrointestinal tract, hands, wrists, and knees were all normal. "Lupus erythematosus" cells were found in the peripheral blood on two occasions but not on two others. Muscle biopsy (left vastus lateralis) was normal.

On three occasions, after withholding prostigmine for five to 12 hours, she was given 1.0 cc. of normal saline intravenously without any improvement. After each injection of saline, 0.5 mg. prostigmine was given intravenously. There was unequivocal improvement of strength of the arms and legs, but this was not pronounced. Each time nausea and abdominal cramps were prominent but there was no fasciculation. On two other occasions after prostigmine withdrawal, 10 mg. Tensilon was given intravenously and the response was similar to that following prostigmine.

In response to ulnar nerve stimulation at a rate of 25 shocks per second, the action potential of the abductor digiti quinti showed a progressive increase in height (figure 3). This was noted when medication had been withdrawn, and the tendency was not corrected by the administration of 0.5 mg. prostigmine intravenously.

On two occasions the administration of a barium mixture for roentgen examination of the esophagus was followed by marked retention in the middle and lower thirds of the esophagus (figure 4), with only slight retention in the pyriform fossae. There was no spontaneous clearing during the next ten minutes and after the administration of prostigmine intravenously, there was only slight and slow emptying.

A dermatologic consultant thought that the skin lesions represented dermatitis factitia. A psychiatric consultant thought that she was fairly stable emotionally and that whatever emotional difficulties she manifested were the

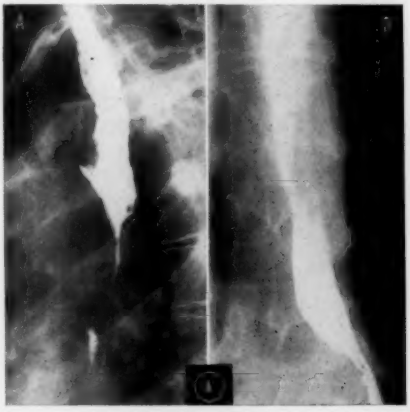

FIG. 4. *Case 4.* Atypical retention of barium in the esophagus. Prior to the administration of prostigmine the barium is suspended in the upper third of the esophagus (*A*). She was then given 0.5 mg. prostigmine intravenously. There was no dramatic clearing but the bolus slowly descended and 10 minutes later was in the lower third of the esophagus (*B*).

result rather than the cause of her muscle symptoms.

Comment: The diagnosis of myasthenia gravis in this woman was initially suggested by her symptoms and physical findings, but a typical response to prostigmine was delayed for almost ten years. Even now she shows only a limited response, although it is unequivocal and consistent and has therefore been considered diagnostic. In addition, the paucity of cranial nerve signs at present, the history of joint symptoms, the positive lupus erythematosus preparation, and the retention of barium in the esophagus after the administration of prostigmine are all atypical. The lack of histologic alteration in the muscle biopsy does not support the diagnosis of polymyositis, but some of the atypical features suggest that she may follow a course similar to that of a patient described by Harvey and co-workers[16] who originally seemed to have myasthenia gravis but subsequently developed manifestations of lupus erythematosus. Her response to quinine or curare at the present time would be of interest, but it has been shown[17] that some patients with myasthenia are not more sensitive to curare and some normal people are just as sensitive as most myasthenics.

MYASTHENIA GRAVIS AND POLYMYOSITIS

Both Eaton and Schwab, previously proponents of the idea that only myasthenia gravis will respond in diagnostic fashion to the administration of prostigmine,[9,10] have recently modified their earlier position.[18] Eaton[18] and others[19–22] have reported that some patients with polymyositis will improve significantly when given prostigmine. Furthermore, there have been reports of patients with more or less typical pictures of myasthenia gravis who had clinical features suggestive of progressive muscular dystrophy.[23–26]

The classification of these patients is difficult because patients with unequivocal myasthenia gravis may have histologic lesions of skeletal muscle which are characterized by necrosis of muscle fibers and an inflammatory response sufficient to constitute a nodular myositis.[12, 27–29] The difficulty is compounded when a concept of polymyositis is offered in which the diagnosis may be made even though an inflammatory cellular response is lacking.[30] Therefore, the differentiation between the two conditions should not be made solely on the basis of histologic alteration, nor the clinical response to prostigmine alone.

Since the etiology of neither myasthenia gravis nor polymyositis is known, it is possible that either syndrome may result from more than one etiology. It is also possible that some patients may have a syndrome which has the characteristics of polymyositis predominantly, but which also has some of the features of myasthenia gravis. The reverse may also be true, while in some patients the syndromes may be so admixed that a clearcut classification is not possible. In essence, there seems to be a syndrome of "myasthenic myositis."

The following patient (also previously reported[12] but not presented in detail) was thought to have myasthenia gravis, although at autopsy she had a devastating myocarditis and there were focal lesions of similar nature in some skeletal muscles.

Case 5.—A 31 year old woman delivered a normal child at the Presbyterian Hospital of New York on April 4, 1943. On November 16 she was readmitted; she had been pregnant again for two months and for the same period of time has had noted dysphagia, dysarthria,

and weakness of the arms. A roentgenogram of the chest revealed an anterior mediastinal mass thought to be a thymoma, but operation was deferred because of the pregnancy.

A prostigmine test was positive and she was started on oral therapy. At home her symptoms persisted although she took 300 mg. prostigmine daily. On April 23, 1944 she was readmitted in an acute exacerbation of symptoms but improved rapidly. On May 1 she delivered a normal infant spontaneously. The immediate postpartum period was uneventful and she was discharged on May 15, still taking 200 mg. prostigmine daily.

On May 19 she was admitted for the third time because of an increasingly severe cough and dyspnea. She was afebrile and in no acute distress, but she was coughing and had some difficulty in raising bronchial secretions. Respiratory movements were rapid and shallow but there was no cyanosis and her lungs were clear. There were widespread cranial nerve palsies and she was unable to speak. There was weakness of the extremities but no atrophy, fasciculation, or tenderness of the muscles. Tendon reflexes and sensation were normal.

She received 1.0 mg. prostigmine parenterally and was then able to take oral medication, 15 mg. at hourly intervals, with parenteral supplements about once a day for brief episodes of dyspnea. On June 2 and 3 she spent sleepless nights, sitting in a chair most of the time, but her lungs remained clear on physical examination and she was afebrile. On June 5 she received an infusion of 5 per cent dextrose in saline. Following this she appeared restless and was given 0.2 gm. Nembutal orally and 0.5 mg. prostigmine parenterally. Thirty minutes later she suddenly became dyspneic and orthopneic. Cyanosis supervened and she became excited. This was not relieved by parenteral prostigmine or paraldehyde. She gradually became comatose and died that evening.

Postmortem examination: 1) There was a large thymoma with no signs of malignancy. 2) Specimens from the diaphragm, intercostal, and cervical muscles all showed occasional necrotic muscle fibers surrounded by small foci of round cells and eosinophils (figure 5A). 3) There was also a subacute diffuse myocarditis (figure 5B) with many focal lesions of variable size, often coalescing. The inflammatory reaction consisted predominantly of small round cells and plasma cells, but there were also some multinucleated giant cells, eosinophils, and polymorphonuclear leukocytes. Within these

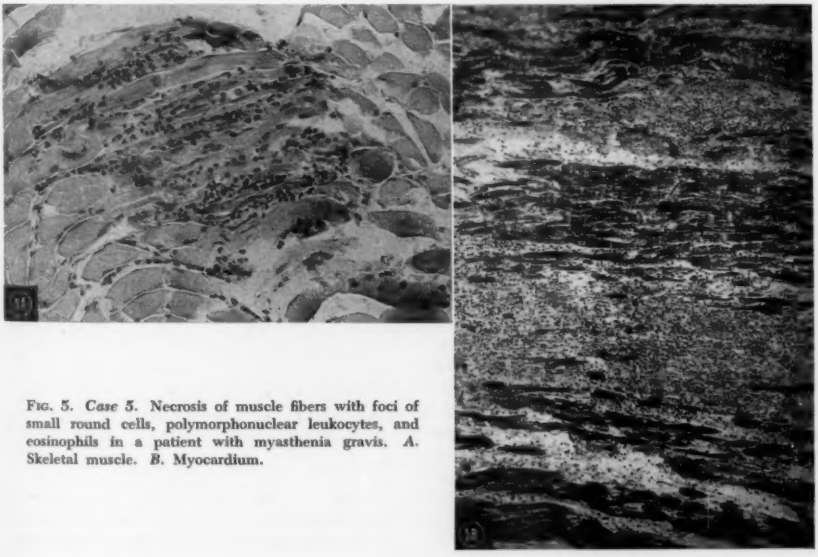

FIG. 5. *Case 5.* Necrosis of muscle fibers with foci of small round cells, polymorphonuclear leukocytes, and eosinophils in a patient with myasthenia gravis. *A.* Skeletal muscle. *B.* Myocardium.

areas, myocardial fibers were necrotic but no organisms were demonstrated. There was cardiac hypertrophy, with a thrombus in the left ventricle. 4) There was evidence of bilateral pulmonary atelectasis, acute pulmonary congestion, and an infarction of the right lower lobe. 5) Small collections of lymphocytes were seen in the thyroid and there was moderate congestion of the liver and spleen. Other viscera were normal and the central nervous system was not examined.

Comment: The clinical picture presented by this woman was that of myasthenia gravis. The myocardial lesions could be coincidental, but the frequency with which they have been encountered in this disease[12,27–29,31] and the similarity of the lesions in skeletal muscle suggest a more intimate relation. It is possible that if she had not been given prostigmine the anatomic diagnosis would have been polymyositis. This syndrome might best be classified as "myasthenia gravis with polymyositis."

MYASTHENIA WITH MINIMAL MANIFESTATIONS: DIFFICULTY OF EVALUATING PROSTIGMINE RESPONSE

Clinical signs of myasthenia gravis may be so mild that there is insufficient weakness to test for a response to prostigmine. In such patients provocative tests with quinine or curare may be of value.[32–34] The following patient illustrates this at a time when he was in partial remission, but it may also be true of patients with very mild myasthenia when they are first seen.

Case 6.—A 37 year old policeman noted the onset of weakness of the right arm while maintaining a prolonged salute. During the next few weeks this was followed by weakness of the left arm, ptosis, dysphagia, weakness of the cervical muscles, and occasional dyspnea at rest. A diagnosis of myasthenia gravis was made elsewhere on the basis of a prostigmine test and he was subsequently treated with small amounts of OMPA (3.0 mg. twice daily), supplemented by 45 to 60 mg. prostigmine. Improvement in strength was significant, but easy fatigability impaired his ability to work and muscarinic symptoms were annoying.

When admitted to the Clinical Center of the National Institutes of Health 17 months after the onset of symptoms, there were no abnormalities other than coarse nystagmus on lateral gaze. Because of the absence of definite signs all medication was discontinued. Slight and inconstant ptosis of the right eyelid appeared and he had some weakness of the muscles of the right shoulder girdle, but these signs were not impressive. A provocative test with quinine was performed 16 days after OMPA had been discontinued. Thirty minutes after the third hourly dose of 0.3 gm. quinine, he developed difficulty in holding his head erect and he had more pronounced weakness throughout the extremities. There was distinct ptosis of the right eyelid and weakness of the facial muscles. He was then given 0.5 mg. prostigmine intravenously and within three minutes there was demonstrable improvement.

ASTHENIA DUE TO PSYCHONEUROSIS

Probably the most frequently encountered nonmyasthenic syndrome in which improvement occurs after the administration of prostigmine is that in which asthenia is related to emotional factors. The fact that such patients usually respond equally well to placebos is not in itself conclusive evidence that myasthenia gravis is not present, since in some patients with myasthenia the response to placebo may be sufficient to be quite misleading and in some circumstances may be dangerous.[28] However, psychoneurotic asthenia does not usually create symptoms referable to the cranial nerves (with the possible exception of "globus hystericus"). The following case illustrates the confusion which may result when cranial nerve symptoms are present, and the usefulness of provocative tests in such patients.

Case 7.—A 21 year old girl was referred to the Clinical Center in 1954 after a diagnosis of myasthenia gravis had been made at a ma-

jor medical clinic. Easy fatigability had limited her activities since the age of five. No specific weakness appeared until she was 20 years old, when she noted dysphagia and difficulty in chewing. She lost 36 pounds during the next five months. Weakness of the hands was pronounced and generalized weakness soon forced her to bed. Drooping of the eyelids and diplopia were reported to vary in severity. Episodes of chest pain and dyspnea occurred from time to time. Because she showed symptomatic improvement after the administration of prostigmine, her personal physician referred her to a nearby clinic for study. There she also had a positive response to a Tensilon test,[35] and the diagnosis of myasthenia gravis was made. She was given prostigmine orally, averaging 350 mg. daily, and improved slightly, but she was still confined to her home, spent most of her time in bed, and required assistance to lift small objects or cut food.

Her past history was unremarkable except that she had complained of pain in the back, abdomen, and legs for many years, persisting despite an appendectomy which had been done because of these symptoms at the age of 15. Photographs of the patient at age one showed ptosis of the left eyelid (figure 6). Her father, the paternal grandfather, and one paternal aunt were also reported to have ptosis of the left eyelid, but photographs were not available.

General physical examination was normal. The cranial nerves functioned well except for ptosis of the left eyelid. Motor examination was difficult to evaluate, since she could move all muscles against gravity, but none against resistance. There was no atrophy or fasciculation and tendon reflexes were all normal. The plantar responses were flexor and abdominal skin reflexes were normal. Equilibratory and nonequilibratory coordination were normal. Sensation was intact. There was no roentgenologic evidence of thymoma.

FIG. 6. *Case 7.* Ptosis of the left eyelid was the only definite abnormality when this woman developed complaints suggestive of myasthenia gravis (*B*). However, she also had ptosis at the age of one year (*A*), and there was a family history of this phenomenon.

Pharmacologic tests were performed on several occasions and active agents were always preceded by an injection of saline or caffeine intravenously. The placebos were usually followed by improvement in the strength of her arms and in grip strength. However, the administration of Tensilon on five separate trials failed to produce any improvement in response to doses of 10 or 20 mg. intravenously. Similarly, she showed no improvement after the administration of prostigmine intravenously on four occasions in doses ranging from 0.5 to 1.5 mg.

She was given quinine orally, 0.3 gm. every hour for six hours. Symptoms of cinchonism occurred and although there was no definite change in her appearance or performance, she reported subjective improvement. Curare was given intravenously on two occasions, 1.5 and 5.0 mg. respectively, and she showed no increased sensitivity. No abnormal fatigue of the action potential of the abductor digiti quinti was noted in response to ulnar nerve stimulation.

Although she averaged 300 to 500 mg. daily of prostigmine during her first week in the hospital, there was no significant change when medication was discontinued for a period of two weeks. On several occasions she failed to answer verbal questions and commands, but she gave other evidence that she was awake and after injections of a placebo she would usually start responding.

Psychologic tests (Wechsler-Bellevue, Rorschach, Thematic Apperception Test) were interpreted to show a lack of integration, failure to adapt, and tendency toward withdrawal, suggesting the presence of a schizophrenic process. A psychiatric consultant expressed the opinion that the patient showed features of both a hysterical disorder and a schizophrenic process.

Comment: The confusing aspects of this girl's problem were the specific na-

ture of her complaints, the presence of ptosis, her tolerance of large amounts of prostigmine, and the response to Tensilon elsewhere. That the ptosis is congenital is attested to by the family history and the earlier photographs. Tolerance for large amounts of prostigmine is probably more characteristic of patients with myasthenia than nonmyasthenics, but some patients with the disease are sensitive to the muscarinic effects of the drug and some people who do not have myasthenia may be unusually tolerant. The original responses to prostigmine and Tensilon were probably placebo effects, since she subsequently failed to show diagnostic responses to prostigmine, Tensilon, curare, or quinine and she did not develop more definite symptoms when prostigmine was discontinued. Psychiatric investigation provided the most direct evidence of the basis of this patient's disorder. The combination of all these facts probably excludes the diagnosis of myasthenia gravis even though it cannot be said with absolute certainty that she may not have some neuromuscular disorder of obscure nature.

CONCLUSIONS AND SUMMARY

Case histories have been presented to illustrate the need for reconsideration of the criteria necessary to make the diagnosis of myasthenia gravis.

It is suggested that any syndrome of muscular weakness not accompanied by alteration of tendon reflexes or sensation in which strength improves significantly after the administration of adequate amounts of prostigmine or Tensilon should be considered to be myasthenia gravis, except when psychoneurosis can be demonstrated to be etiologically important. The diagnosis becomes more certain if there have been remissions in the past, if weakness is aggravated by fatigue and improved by rest, and if symptoms referable to the cranial nerves are prominent, but none of these features individually is necessary.

The presence of inflammatory lesions in skeletal muscle, macroscopic muscular atrophy, or thyrotoxicosis does not automatically change the diagnosis from myasthenia gravis to polymyositis, muscular dystrophy, or thyrotoxic myopathy. Although some clinical features may suggest one of these alternative diagnoses in such cases, it might prove least confusing to regard any prostigmine-responsive syndrome as myasthenia gravis and to recognize that myasthenia may occur in association with other disorders.

It is not necessary to assume that all prostigmine-responsive syndromes will prove to have the same etiology, or even the same physiologic disturbance. There is suggestive evidence that the association of myasthenia gravis with thymoma,[36,37] thyrotoxicosis,[38] myositis,[27–29] and perhaps bronchial carcinoma[20] or epilepsy[28] is more than coincidental and possibly of etiologic significance. Whether the pathophysiology which produces myasthenic symptoms is the same in all of these conditions is unsettled.

The converse of the above postulate is not necessarily true, since some patients with a clinical syndrome identical to that described for myasthenia gravis may never respond to prostigmine in diagnostic fashion. Whether or not this is actually the same disease cannot be stated, but when a patient presents a disorder characterized solely by weakness of the extremities and of respiratory and cranial muscles, when the severity fluctuates and autopsy fails to provide an anatomic diagnosis, it is difficult to use

any label other than myasthenia gravis, regardless of the lack of response to prostigmine. The existence of such cases creates a problem in classifying and understanding these cases of polymyositis and asthenic syndromes associated with hyperthyroidism which do not respond to prostigmine.

The possibility that some patients with myasthenia may never respond satisfactorily to prostigmine or Tensilon does not detract from the general usefulness of these drugs as diagnostic agents. Furthermore, some patients who initially seem to belong in this category may subsequently respond in the characteristic manner, so that repeated tests may sometimes be rewarding.

The value of having a therapeutic test is emphasized by reports of patients with fatal syndromes of muscular weakness who did not receive prostigmine. The diagnosis of myasthenia gravis seems reasonably certain in such untreated disorders when they are associated with thymomas[27,39,40] but there may be doubt when there is no thymic tumor. It is likely that there are many unreported cases of this nature.

Provocative tests with curare and quinine may be valuable when the manifestations of myasthenia are mild, when emotional factors are significant, or when the effects of prostigmine are difficult to evaluate. However, quinine and curare may be dangerous and should not be used when patients are seriously affected. Furthermore, it has been shown that the tests may not be absolutely specific.[17] In mild and equivocal cases the use of placebos prior to therapeutic tests is of value.

These considerations exemplify some of the difficulties of classification and diagnosis. Differences of opinion are likely to persist until more fundamental information about the pathogenesis of myasthenia becomes available and permits a rational concept of this disorder. It has been suggested by several writers that myasthenia gravis may be a syndrome of varied etiology and not a disease entity.

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Syndrome of Intermittent Insufficiency of the Basilar Arterial System

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TRANSIENT EPISODES of focal neurologic abnormalities occurring in the middle or older age groups and attributed variously to so-called vasospasm or small strokes are common and have been known to neurologists for many years. Despite considerable study, the exact pathogenesis of these has not been made clear. It is not the purpose of this communication to deal at length with data concerning the causation of these transient states of dysfunction of the central nervous system, although ischemia is assumed to be the factor fundamental to the actual production of symptoms. Rather, we wish to point out that there is a group of patients who, for one reason or another, have transient episodes presumably due to insufficient blood flow through various portions of the basilar arterial system.

These phenomena have never been adequately grouped. This complex of periodic transient symptoms might be termed "the syndrome of intermittent insufficiency of the basilar arterial system."[1] Although in some cases the diagnosis can only be suspected, in many instances the diagnosis can be made if one is alert to the possibility. It is our impression that these periodic phenomena due to insufficiency of the basilar artery may be more common than is generally believed. It also appears that this symptom complex is a common historic feature in patients who succumb to closure of the basilar artery by thrombosis. Once the diagnosis of occlusion of the basilar artery is established, serious neurologic abnormalities are usually present and the prognosis is grave. If treatment is to be adequate, it must in a sense be preventive or anticipatory, since there is no replacement for infarcted cerebral tissue. The first requisite for any treatment is early diagnosis.

The transitory episodes under discussion may occur for months or years. They may be brief, lasting several minutes, or they may last several hours. Most last about 15 to 30 minutes. Between these spells the patient is well. Examination between the episodes reveals normal findings, while during an attack objective abnormalities are demonstrable. Although there are instances in which minor residual neurologic difficulty remains, we have chosen to look on most

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of the latter as instances of permanent damage to the brain, presumably from actual thrombosis with infarction, and not from episodic ischemia alone.

The symptoms include weakness or numbness of a limb or limbs, visual abnormalities, and pseudobulbar or bulbar phenomena. Several cases are given to illustrate some of the various manifestations. Normal laboratory and other noncontributory findings have been eliminated from the case reports.

ILLUSTRATIVE CASES

Case 1.—A 62 year old farmer had had episodes of vertigo lasting five to 30 minutes over a two-year period. Three days prior to admission he had an episode of vertigo and slurred speech. While driving to a nearby town, he again had trouble talking and this lasted 30 minutes. That night he had an attack during which his vision was dim and he was vertiginous. Then he was well until the day of admission when he had several attacks, one of staggering gait and vomiting, another of dysarthria, and another of left hemiparesis. Shortly before admission he began to have trouble focusing his eyes, and examination revealed almost complete paralysis of ocular movement, miotic pupils, dysarthria, right peripheral facial-nerve palsy, left hemiparesis and hemianesthesia, and weakness of protrusion of the tongue. He soon lapsed into coma and died three days later. Necropsy revealed thrombosis of the basilar artery in its distal two-thirds, and infarction of the pons, particularly the right side, the right side of the midbrain, and the right cerebellar hemisphere.

Case 2.—The patient was 74 years old at the time of his death in 1953. In 1952 he had several episodes of vertigo and on May 1, 1953, while driving, he had a five-minute episode of vertigo and nausea. The next day on arising he felt dizzy and vomited. Later, his vision was poor in the right homonymous half field during a 30-minute period. Still later that day an episode occurred wherein his speech was slurred. The following day he had a transient attack of dysphagia from which he likewise recovered. He was admitted to the hospital on May 9, 1953, soon after the development of poor use of the right limbs and ptosis of the right lid. Neurologic examination revealed, in addition, nystagmus on lateral gaze and anisocoria (right larger). The next day the limbs were normal, but he had dysarthria and the nystagmus was more pronounced. On May 11 a right homonymous hemianopsia was demonstrable. Two days later he was comatose, with flaccid limbs and bilaterally positive Babinski signs. He died on May 15 and necropsy disclosed thrombosis of the basilar and left posterior cerebral arteries. There was massive infarction of the pons, midbrain (more on the left), left occipital lobe, and the posterior portion of the left thalamus.

Case 3.—This patient was 63 years old when he died in 1953. During the summer of 1950 he had many "blackout spells" without actually losing consciousness completely. These stopped, but in 1951 he had episodes of tingling in the hands that lasted ten to 30 minutes. During the summer of 1952 he had a myocardial infarction and noted transient slurring of speech and unstable gait at that time. In May 1953 he began to have spells of confusion, mumbling speech, and dimness of vision. These occurred two or three times a day and lasted 15 to 30 minutes. These continued, and early on June 11 he had an attack of right hemiparesis, including the lower half of the face, with positive Babinski sign, dysarthria, and vomiting. He was observed during this attack when the above abnormalities were noted, and within an hour he was strikingly normal. He was sent to the hospital but on the way became comatose and died late that day. Necropsy revealed laminated thrombosis of the distal portions of the vertebral and the basilar arteries and infarction of the pons.

Case 4.—About two weeks prior to admission, a middle-aged lady began to have attacks of vertigo. These lasted five to ten minutes and occurred two or three times a day. Between these episodes she was well. Several days after the onset of these spells, she had an attack of left hemiparesis lasting 15 to 20 minutes. For the next week she had frequent episodes of hemiparesis, some involving the left limbs and some the right limbs. The day before admission dysphagia occurred and on admission she was stuporous. She died three days later. Necropsy revealed thrombosis of the basilar and vertebral arteries and hemorrhagic infarction of the pons, particularly the left side, and infarction of portions of the left calcarine area.

In cases 1 to 4, the patients had thrombotic occlusion of the basilar artery and infarction within its field of supply. In some instances, the infarction occurred in areas previously presumed to have had episodic insufficiency of blood flow. The basilar artery was thickened and arteriosclerotic and contained a recent thrombus of an age consistent with the clinical history. Review of the protocols indicates transient episodes of neurologic dysfunction early in the course of the illness, and this phase would then be the syndrome of intermittent insufficiency of the basilar arterial system. From the point in time when persistent neurologic deficits remain, it is assumed that infarction, probably due to thrombosis within this field, was present. In these cases death ensued and was related to thrombosis of the basilar artery itself.

Case 5.—A 60 year old man was seen because he had had "spells" for about two years. These attacks consisted of the sudden onset of vertigo, diplopia, and dimness of vision. Each lasted several minutes and their frequency had gradually increased until they were occurring three to four times a week. In an occasional attack there were also numbness of the left limbs and poor use of the left hand. On one occasion the speech was slurred. Neurologic examination on admission was normal.

Case 6.—Ten days before admission a 56 year old man began to have episodes during which he had dysarthria, dysphagia, and quadriparesis. These attacks lasted from several minutes to an hour and were of varying severity. Their frequency increased and on the day of admission he had 12 of them. Examination during an attack revealed him to be dysarthric, dysphagic, and quadriplegic, with hyperactive stretch reflexes and bilaterally positive Babinski signs. After the attack the results of neurologic examination were normal.

Case 7.—During the two years prior to admission, a middle-aged man had three episodes wherein he suddenly became nauseated and "blacked out." He was unconscious one or two minutes. Four months before, he began to have transient attacks of blurring of vision and numbness of the right limbs. Once there was a five-minute period of complete anopsia in the right half of the visual field only. On one occasion there were sudden paralysis of the right limbs and anarthria; these lasted 15 minutes. On the day of admission he had an attack of quadriplegia and anarthria, an attack of left-sided paralysis, and three attacks of right-sided paralysis with slurred speech, each attack lasting some 15 minutes. One of the latter was observed, during which he had marked dysarthria with accurate word choice and no conceptual defect and a right hemiplegia with a positive Babinski sign. The entire episode lasted about 15 minutes, following which he was normal.

Case 8.—Three months prior to admission, a 50 year old man began having episodes of numbness and tingling of the tongue, right side of the face, and right upper limb, and mushy speech. Each lasted five to 15 minutes and he was symptomless between episodes. Their frequency gradually increased until they occurred three times a day. On one occasion the left side of the face and left hand were involved. Dr. L. M. Eaton observed the patient during one episode and noted severe dysarthria (not aphasia) and decrease in the alternate motion rate of the right hand. After the attack the results of the neurologic examination were normal.

In cases 5 to 8 the patients had intermittent symptoms highly suggestive of insufficiency of the basilar arterial system. These four patients received anticoagulant medication with prompt relief of their symptoms and have been reported elsewhere in this regard.[2]

COMMENT ON CASES

A review of the protocols presented herein reveals many symptoms. Singly they may all be explained by poor blood flow somewhere in the field of the basilar artery. When grouped together, these symptoms form a pattern which would appear to be explained by abnormalities within this field alone. That ischemia is fundamental is implied from

the findings in those cases in which necropsy was performed and from the character of the attacks.

The symptoms may conveniently be listed as 1) weakness of the limbs, 2) visual or oculorotatory abnormalities, 3) pseudobulbar or bulbar phenomena, 4) numbness, and 5) miscellaneous.

Weakness or poor use of a limb consisted variously of monoparesis, hemiparesis, or quadriparesis. The occurrence of hemiparesis on the right side in one attack and on the left in a different attack is highly suggestive of basilar arterial insufficiency.

Ophthalmologic abnormalities were of two types — visual dimness and oculorotatory trouble. Homonymous hemianopsia, or bilateral homonymous hemianopsia,[3] recalled as dimness of vision, was frequently present. Presumably, monocular amaurosis does not appear in this syndrome. The occurrence of diplopia, somewhat less frequent historically, may serve to establish the diagnosis.

The pseudobulbar or bulbar phenomena of dysphagia and dysarthria were common. No expressive aphasic dysfunction was noted. Dysarthria and dysphagia do not necessarily have to occur simultaneously in a single attack; in fact, it is surprising how often they may be dissociated.

Numbness may appear in a limb or on one side of the body or face. Like hemiparesis, where numbness alternates from side to side in different attacks, this is characteristic.

In the miscellaneous group, the symptoms of vertigo and confusion were noted. Episodes of vertigo probably are the most frequent single symptom. It was not associated with tinnitus or loss of hearing. Although vertiginous attacks are common alone, they may be associated with another symptom such as nausea or vomiting. Episodes of vertigo and dizziness and of transient confusion or excessive sleepiness, in themselves, are often difficult to interpret. Within the framework of other symptoms, they take on a special meaning.

DISCUSSION

A review of the cases in the excellent study by Kubik and Adams[4] on occlusion (proved at necropsy) of the basilar artery reveals that eight of 11 patients with thrombosis had previous episodes consisting mainly of dizziness, headache, facial or limb weakness, and dysarthria. In their seven patients with embolism, only one had previous neurologic symptoms. Their study pointed out that occlusion of the basilar artery is by no means rare and that the diagnosis may often be made during life.

Silversides[5] presented 22 cases of thrombosis of the basilar artery (proved at necropsy). In these, nine patients had recurrent premonitory symptoms suggestive, as he wrote, of "periodic insufficiency of blood flow to the brainstem." He thought that a stenotic basilar artery was a prime factor in the causation of these.

Denny-Brown,[6,7] in commenting on transient cerebrovascular episodes in general, expressed the opinion that stenosis of either the carotid or the basilar artery played an important part in the genesis of such episodes.

A recent personal review[8] of cases of thrombosis of the basilar artery indicated that about two-thirds of the patients had episodes of neurologic symptoms prior to their final illness.

DIAGNOSIS

A single episode or several similar

attacks consisting of only a few symptoms may not be diagnostic. When many appropriate symptoms are present in a single attack, or when numerous attacks vary somewhat around a central, more stereotyped core, the symptoms can be attributed to intermittent insufficiency of the basilar arterial system.

The symptoms (or abnormal physical signs during an attack) vary, depending on the region involved. Since the region supplied by the basilar artery and its branches is relatively complex, many symptoms may occur. Each is nonspecific. When a pattern is formed by the occurrence of the same symptoms on opposite sides of the body in definite and separate attacks, the diagnosis is suggested, and with the addition of dim vision, dysarthria, dysphagia, diplopia, or vertigo, the diagnosis is probably correct.

It is to be emphasized that care need be taken by appropriate examination and observation to exclude other more likely causes of transient neurologic symptoms. Frequently difficulty arises in separating insufficiency in the basilar system from that in the carotid arterial system. In the latter, hemiparetic episodes remain one-sided and monocular dimness of vision may occur. Aphasia or other conceptual defects occur, as would be expected when the dominant side is involved. Dysphagia, slurred speech, and diplopia point to the brainstem.

Aside from vascular etiology, convulsive disorders in their various manifestations and various expanding mass lesions presenting intermittent symptoms must be considered. The diagnosis may not always be immediately clear and further observation may be necessary.

The course of this condition is not known. It is possible that some persons have these spells for a while and then recover. The patients who have come to our attention apparently had serious conditions, and probably the episodes were increasing in frequency or severity. It is our feeling that many patients with this syndrome may later have thrombosis with extension of this into the main channel, producing serious neurologic deficit.

In many patients who subsequently die of thrombosis of the basilar artery, the phase of intermittent insufficiency forms the early portion of the total course of the disease. The frequency of the spells tends to increase, and eventually severe and permanent damage occurs.

Our main interest in the pattern of attacks and the early historical aspects of basilar system disease is the concept of recognition early in its course, and it is to this that we wish to draw attention. This recognition would seem to be important, since the symptoms of intermittent insufficiency appear to be relieved by the administration of anticoagulant drugs.[2]

SUMMARY

There is a group of patients with cerebrovascular disease who suffer periodic and transient episodes of neurologic dysfunction, consisting, in various combinations, of weakness of the limbs, dimness of vision, diplopia, dysphagia, dysarthria, vertigo, numbness, and confusion. The occurrence of these symptoms in sharply episodic form and the pattern thus evolved appear to be due to temporary ischemia within the field of the basilar artery. For this syndrome the term "intermittent insufficiency of the basilar arterial system" is suggested.

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■ If we now examine what might be the disposition of the conductors of sensitive impressions in the spinal cord, we find that either they might be scattered without any order at all, or they might have one or the other of these two kinds of arrangements: 1st. They might be disposed in such a manner that the anterior parts of the body, the middle parts and the posterior parts, would each have a peculiar place in the cord. 2nd. They might be arranged so that each small portion of the conducting part of the cord, would contain conducting elements from the anterior, the middle, and the posterior parts of the body. Now, if we take the results of the above experiments, we find that they agree with this last supposition, and not with the others. If there was no order in the disposition of the elements conducting sensitive impressions, in the spinal cord, we should not have found changes taking place exactly in the same measure in all the parts of the body behind the section — i. e., in the skin, in the trunks of nerves, and in the viscera of the abdomen. If the anterior parts of the body had their conductors of sensitive impressions crowded together, as well as the posterior and middle parts also, we should have found that certain sections produced anaesthesia in certain parts, and not in others, while on the contrary we find anaesthesia, when it first appears, beginning everywhere at the same time, and when it increases, and also when it becomes complete, we find that it is so everywhere. We must, therefore, admit that elements representing the various parts of the body exist in the various portions of the spinal cord from behind forwards in the conducting zone of this organ. This explains clearly why so complete loss of sensibility is so rare in diseases of the spinal cord.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Pupillary Reflex Shapes and Topical Clinical Diagnosis

Otto Lowenstein, M.D.

IN CLINICAL EXAMINATIONS of the pupils, most neurologists and ophthalmologists are satisfied with the statement that both pupils are round, of "average" and equal size, and react promptly to light and near vision. When these characteristics are present the pupils are called "normal." Such limited examinations reveal only a small fraction of the cases with pupillary pathology, namely those in which the pupils are grossly deformed, in which the reflex movements are markedly sluggish, inextensive, or absent, or in which anisocoria is visible. They do not make use of the sensitive and accurate diagnostic system which can be derived from the careful analysis of the pattern of pupillary movements.

Analysis of reflex shapes is not new to the clinician. The patellar reflex, for example, is not described solely as to unilateral or bilateral increase, decrease, or absence. Equally important are observations as to the shape of the reflex, whether the reflex is spastic or clonic, inhibited or exaggerated by psychological or other factors, and whether it is limited to the proper effector muscle or muscle groups. Such observations are routinely included in the findings of clinical examinations.

Pupillary movements and reflexes, similarly, may not only be slower or less extensive than normal. They may show an even greater variety of pathologic reflex shapes than those seen in deep reflexes.

The iris is an ideal indicator of autonomic reflex activity. This membrane with its freely floating edge is unimpeded by mechanical weights, and its movements, unlike those of other autonomic structures, can be recorded without even touching the body. All pupillary reactions, both of contraction and dilation, are typically integrated autonomic reflexes. Functional or organic damage to the nervous centers or pathways which normally control the iris results in characteristic changes of the reflex pattern. It is the purpose of this paper to describe the abnormalities of the reflex pattern most frequently encountered in pupillographic examinations and to show their significance in topical diagnosis.

METHOD

The pattern of a pupillary reflex depends not only on the strength and the

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duration of the stimulus, but also on the equilibrium of pupilloconstrictor and pupillodilator impulses present in the iris at the moment of stimulation. It is therefore necessary to standardize the experimental conditions and to eliminate as far as possible interfering extraneous sensory or emotional stimuli. The experimental conditions observed for clinical examinations of the pupillary reaction to light are summarized as follows:

The patient, comfortably seated, with his head supported by a headrest and chinrest, fixes upon a weak red light of 10 mm. diameter, placed at an angle of 15° above and at a distance of 10 feet in front of his eyes. The illuminating light necessary for the recording of the pupillary images on infra-red-sensitive film, is furnished by two 6V, 2.75A tungsten bulbs, equipped with condensors and dark red-infrared filters (Wratten 88A). After six minutes of adaptation to darkness, the right, left, or both eyes are exposed to series of light stimuli of average (15 foot-candle) or of low intensity (usually about 0.2 foot-candles, occasionally up to 4 foot-candles). The duration of these light stimuli is one second, the dark interval between stimuli is three seconds. The details of pupillographic procedure have been described previously.[1]

Our clinical material concerned with pupillary pathology includes approximately 2,500 cases. Normal human values were derived from about 300 subjects. Most of them were examined repeatedly under various conditions. In addition, 129 cats and 40 monkeys were used. They were examined many times, both before and after experimental lesions were placed at specific sites within the centers and pathways of pupillary control. From this material, eight clinical cases have been selected. They are representative of the syndromes most frequently encountered in clinical pupillographic work. Our general statements, however, are based on the entire material at our disposal.

RESULTS

I. *The shape of the normal reflex to light.*

Many factors influence the shape of the light reflex. Anatomically speaking, many neurons, afferent, central, and efferent, are involved.

The reflex arc proper.

1. Retinal impulses run through the optic nerve, optic chiasm, and optic tracts to reach the pretectal area on each side via the brachia of the superior colliculi (figure 1.-1).

2. From the pretectal area on each side, half of the impulses course around the sylvian aqueduct to reach the Westphal-Edinger nucleus on the same side, while the other half cross in the posterior commissure to reach the Westphal-Edinger nucleus on the opposite side (figure 1.-2).

3. Efferent fibers from the Westphal-Edinger nucleus run with the third cranial nerve to the ciliary ganglion (figure 1.-3).

4. The short ciliary nerves, arising from the ciliary ganglion, innervate the iris sphincter.

Inhibitory factors.

Inhibition of the third nerve nucleus is mediated by at least three paths:

1. Over direct pathways from the cortex (probably area 8) to the third nerve nucleus (figure 1.-5 and 12).

2. From the cortex via the thalamus and hypothalamus to the third nerve nucleus (figure 1.-5, 6, 7, 12).

3. From every sensory nerve, with the

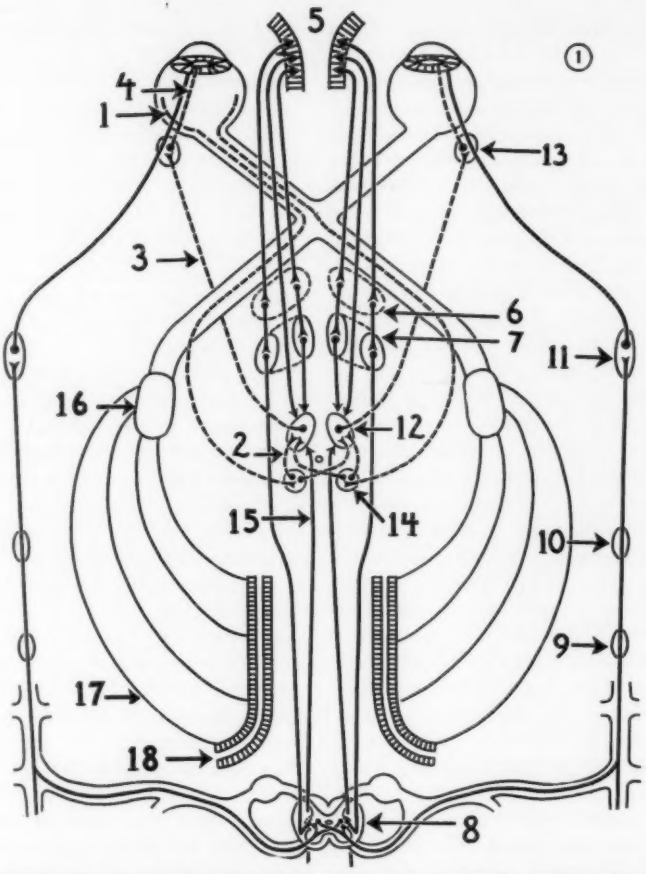

FIG. 1. *Scheme of nervous centers and pathways taking part in shaping the pupillary reflex to light.* 1: First afferent neuron of pupillary light reflex arc, from retina → optic nerve → optic tracts → brachia conjunctiva of superior colliculi to pretectal area on each side. 2: Second afferent neuron of pupillary light reflex arc, from pretectal area of each side to homolateral and heterolateral third nerve nucleus. 3: First efferent neuron of the pupillary light reflex arc (third nerve). 4: Short ciliary fibers to iris sphincter. 5: Cortex (probably area 8). 6: Thalamus. 7: Hypothalamus. 8: Budge's center in lower cervical and upper thoracic cord. 9: Inferior cervical ganglion. 10: Middle cervical ganglion. 11: Superior cervical ganglion. 12: Third nerve nucleus. 13: Ciliary ganglion. 14: Pretectal area. 15: Afferent inhibitory fibers traveling in reticular formation to third nerve nucleus. 16: Lateral geniculate ganglion. 17: Optic radiation. 18: Visual cortex.

exception of the optic nerve, over a diffuse afferent system in the reticular formation to the third nerve nucleus (figure 1.-15).

Antagonistic factors.

The iris dilator muscle acts as an antagonist to the pupillary sphincter. It is innervated by impulses traveling from the cortex via the thalamus to the sympathetic center of Karplus and Kreidl in the posterior hypothalamus, and from there over the cervical cord and periph-

eral cervical chain to the eye (figure 1.-5, 6, 7, 8, 9, 10, and 11).

When all of these factors function normally, the pupillogram of the normal reaction to light shows the shape seen in figure 2.-A. The dark-adapted eye is exposed to a light stimulus of 15 foot-candle intensity and one second duration. After a latency period of about 0.2 second, the pupil contracts and redilates some time after the light stimulus has ended. The redilation occurs in two phases, a first (faster) and second (slower) one.

The contraction movement, as well as the two redilation phases, are not performed at an even rate, but occur in waves of smoothly increasing and decreasing speed. The normal acceleration and deceleration are particularly well demonstrated when the differential curve is drawn. It is derived from the original pupillogram by plotting against time (0.1 second) the extent of contraction or dilation that occurs within each successive 1/10 second. This shows three waves of increasing and decreasing speed of motion (figure 2.-A1). The C-wave represents the phase of increasing and decreasing contraction speed, the D- and E-waves the first and second phases of increasing and decreasing redilation speed.

II. *Pathologic changes in the pupillary reflex pattern.*

When an experimental or clinical lesion injures one of the pupillary centers or pathways, the normal reflex pattern is modified in a manner characteristic of the site of the lesion.

Lesions of the peripheral sympathetic system.

If the cervical sympathetic path is damaged, either pre- or postganglionically, part of the system which normally antagonizes the contraction to light is eliminated. After adaptation to darkness, the sympathectomized pupil is smaller than the normal one. It contracts somewhat faster to light, and the second redilation wave (E-wave) is absent (figure 2.-B and B1). Psychosensory dilation is greatly reduced in extent and speed.

Lesions in the diencephalon or its connections to the midbrain, close to the midline.

If a lesion is located fairly close to the midline in the diencephalon or its connections to the midbrain, the third nerve nucleus may be released from the inhibitory impulses from the cortex, thalamus, and hypothalamus. This has a profound effect on the shape of the pupillary reflex to light. After adaptation to darkness the pupil is seen to be even smaller than in cases of peripheral sympathectomy. The reflex to light adopts a square wave shape and is less extensive than normal. The small extent of the contraction to light is due to the small initial size of the pupil and not to a lack of parasympathetic strength. This is demonstrated in the differential curve, where the speed of contraction is seen to be greater than normal. The maximal constriction is reached almost immediately. The pupil remains fully contracted until some time after the light stimulus has ended. This square-wave reflex shape, which is characteristic of diencephalic conditions, has been named "tonohaptic" reflex shape[2] (figure 2.-C and C1).

Psychosensory dilation is generally not disturbed in cases with tonohaptic light reflexes, because the inhibition pathways to the third nerve nucleus lie closer to the midline than the more lateral pupil-

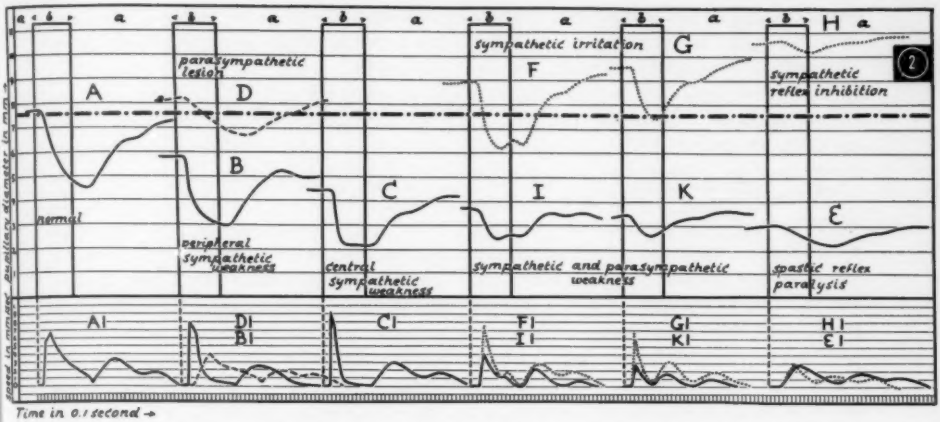

FIG. 2. *Dynamic structure of normal and pathologic pupillary light reflexes.* In the original pupillograms (first line, A-K), pupillary diameter is plotted (in mm.) against time (in 0.1 second). The dash-dot line represents the diameter of the normal dark-adapted pupil. *a:* darkness; during the time outlined by the areas *b*, the patient's eyes were exposed to light stimuli of 15 foot-candle intensity and one second duration. The differential curves (second line, A1-K1) show the speed (in mm./second) at which pupillary contraction and dilation occur within each reflex. They are derived from the original pupillograms by plotting against time (in 0.1 second) the extent of motion that occurs within each successive 1/10 second. A: The normal light reflex. After latency period of about 0.2 second, the pupil contracts, then redilates after the light stimulus has come to an end. The differential curve (A1) shows three waves of increasing and decreasing speed of motion. The C-wave corresponds to the contraction, the D- and E-waves to the first (faster) and second (slower) phases of redilation (cf. text). B-K: Pathologic reflex shapes, and their respective differential curves B1-K1 (for details, cf. text). The conditions shown are B: damage to the peripheral sympathetic chain; C: diencephalic lesions; D: nonirritative nuclear or postnuclear third nerve lesions; E: irritative nuclear or prenuclear third nerve conditions; F, G, and H: central sympathetic irritation; I and K: generalized degenerative conditions involving both interbrain and midbrain. In these pathologic conditions, the changes in reflex pattern are permanent and irreversible. The reflex shapes shown in B, C, I, K, and E can also be found in normal subjects, transitorily and reversibly, as stages of physiologic fatigue, the shapes F, G, and H as a result of strong emotional stimuli.

lary dilation pathways (figure 1).

Nonirritative partial lesion of the third nerve nucleus.

In cases with nonirritative partial lesions in the third nerve nucleus or peripheral to it, after adaptation to darkness the pupil of the injured side is normal in size or very slightly enlarged. When the pupils are examined in diffuse room illumination, the pupil on the side of the lesion may be much larger than the normal pupil. The reflex to light is sluggish, inextensive, and preceded by a prolonged latency period (figure 2.-D and D1). Psychosensory dilation is undisturbed and as extensive as that of the normal dark-adapted pupil.

Nuclear or prenuclear irritative lesions of the third nerve.

In cases with an irritative nuclear or prenuclear third nerve lesion, the dark-adapted pupil is smaller than normal and reacts sluggishly and inextensively to light (figure 2.-E and E1). Dilation in response to psychosensory stimuli may be normal in cases in which the reaction to light is absent. When the pupil is small and the light reflex is highly reduced or absent while the reaction to near vision is preserved, it is called Argyll Robertson pupil (reflex pupillary immobility).

Central sympathetic irritation.

In cases of central sympathetic irrita-

tion, the pupils are larger than normal, both in light and in darkness. When sympathetic irritation increases, the size of the pupil increases and the light reflex assumes a W-shape or V-shape. In pronounced irritation, the contraction to light may be absent due to complete inhibition. W- and V-shapes of the light reflex in large pupils are not due to parasympathetic weakness; the contraction starts with a normal latency period and normal speed, but the powerful sympathetic antagonist overcomes the contraction impulses and forces the pupil to redilate prematurely after the main contraction force is expended (figure 2.-F and F1, G and G1). Psychosensory dilation is normal or exaggerated in cases with central sympathetic hyperirritability.

Parasympathetic and sympathetic weakness.

W- and V- reflex shapes may also be seen in small pupils, when both the sympathetic and parasympathetic are weakened. In the case of large pupils, there is an unstable equilibrium of two strong antagonists; in the case of small pupils, there is a similar equilibrium of two weak antagonists. The shape of the reflexes is identical, but the extent and speed of motion as well as the pupillary diameters are different in the two conditions (compare figure 2.-F, F1 and G, G1 with I, I1 and K, K1). Psychosensory dilation is usually normal in cases of sympathetic and parasympathetic weakness.

III. *Functional changes in the pupillary reflex pattern.*

It is of general physiologic interest and of clinical importance that all reflex shapes, described above as resulting from pathologic conditions at specific sites in the nervous system, may appear as transitory and reversible phenomena as a result of physiologic fatigue or excitement.

Autonomic reflex activities, such as the pupillary reflex to light, may be fatigued or under certain conditions even exhausted.[3] A number of stages can be recognized in the process of fatigue. In the earliest stage of fatigue the reflex pattern is the same as the one found in cases of peripheral sympathetic impairment. This is an expression of the elimination of sympathetic cortical centers which normally send impulses to the antagonistic pupillary dilator muscle via the thalamus, hypothalamus, cervical cord, and sympathetic chain. In the next stage of fatigue, tonohaptic reactions occur; this is due to elimination of diencephalic centers which normally inhibit the third nerve nucleus. When fatigue advances further, parasympathetic weakness is added to the sympathetic weakness. The pupil becomes smaller, the light reflexes inextensive, showing small w- and v-shapes. In the next stage, the miotic pupil reacts inextensively and sluggishly, and finally, in cases of complete exhaustion, it may fail to react at all.

Fatigue, therefore, is an ordered sequence of events, whereby the functions of specific nervous centers are diminished and finally extinguished in a given order. From pupillary studies, a general law of autonomic nervous fatigue was formulated: All fatigue is predominantly central in origin. Cortical centers fatigue sooner than subcortical centers, the sympathetic earlier than the parasympathetic.[3]

In contrast to pathologic reflex patterns which are permanent and irreversible, physiologic fatigue can readily be reversed by rest. In addition, complete

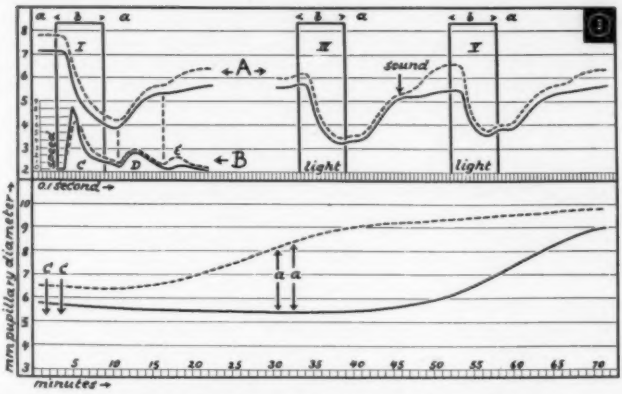

FIG. 3. *Case 1. Injury to right peripheral (postganglionic) sympathetic fibers.*

First line, A: In the original pupillogram, the pupillary diameters (in mm.) are plotted against time (in 0.1 second); the solid line represents the right, the broken line the left pupil. The first, fourth, and fifth of a continuous series of light reflexes are shown. In darkness (a), the right pupil is smaller than the left one. During the contractions to light, (b), this anisocoria is diminished and finally disappears altogether (fifth reaction). It reappears during the second phase of redilation. The response to the sound stimulus is normal on the left but absent on the right side.

First line, B: In the differential curve, the speed of contraction and redilation is plotted (in mm./second, small numbers) against time (in 0.1 second). The contraction speed shows an earlier and higher peak, and the second redilation wave (E-wave) is almost absent on the right (injured) side.

Second line: The pupillary diameters are plotted (in mm.) against time (in minutes). At each of the arrows *c*, one drop of cocaine hydrochloride (2%) is instilled into each of the conjunctival sacs. 15 minutes later, the left pupil begins to dilate, while the right pupil remains unaffected. At each of the arrows *a*, one drop of adrenaline hydrochloride 1:1000 is added to each eye. About 15 minutes later, the right pupil begins to dilate.

reintegration of the normally fatigued or exhausted function can also be induced at any stage by sympathetic stimulation, provoked by sensory stimuli, emotional excitement, or even spontaneous thinking. This phenomenon has been termed the "psychosensory restitution phenomenon."[1a] It is not limited to pupillary reflexes, but is a general principle of reintegration of fatigued or exhausted nervous centers. The absence or diminution of the psychosensory restitution phenomenon is generally associated with tonohaptic reflex shapes and, as these, another sign of diencephalic lesion.

CLINICAL APPLICATION

Out of the extensive clinical material studied, eight cases will be described. They are representative of the clinical lesions more frequently encountered.

Case 1.—Pain in the distribution of the first and second trigeminal branches, with impairment of the sympathetic (postganglionic) fibers on the same side.

The patient, a 54 year old man, had a 20 year history of paroxysmal pain. The pain started at the supraorbital foramen and manifested itself first in short lightning flashes of pain. The paroxysms gradually increased in severity and extent. They had commenced in the first division, gradually extended into the second. Light touches of the hypersensitive skin frequently caused the immediate occurrence of an attack. It was reported that during attacks of headache, his right forehead showed beads of sweat, the right eye teared excessively, and the hypersensitivity to touch extended to his right scalp. Anisocoria was noted with the right pupil smaller than the left, but ocular movements and pupillary reflexes were reported to be normal. The spinal fluid was normal.

Neurologic examination showed that both

supra- and infraorbital points of the fifth nerve were hypersensitive to pressure on the right, but not on the left side. The corneal reflex was slightly more pronounced on the right than on the left side; the right half of the face in the area of the first and second trigeminal branches was more sensitive to touch and pain than the left.

Pupillographic studies: The left pupil was normal. The right pupil showed all the features of damage to the peripheral postganglionic sympathetic path (figure 3):

1. In darkness, it remained smaller than the left pupil.

2. This anisocoria disappeared during contraction to light and reappeared in the second phase of redilation (E-wave of differential curve). The contraction to light was more rapid than normal; the differential curve showed a slightly early peak of speed which was higher than normal.

3. The right pupil failed to dilate in response to psychosensory stimuli, so that the anisocoria became enhanced after a sound stimulus.

4. Cocaine failed to dilate the right pupil, which did dilate when 2 drops of adrenaline hydrochloride 1:1000 were added to each eye.

Case 2.—Unilateral lesion of the third cranial nerve in a case of multiple sclerosis.

The patient was a 32 year old woman with multiple sclerosis who three days before examination began to have blurred vision on the left side. Neurologic examination showed absent abdominal reflexes and increased deep reflexes on the left side, while the deep reflexes on the right side were normal.

Pupillographic examination showed the typical picture on an incomplete lesion of the efferent third nerve (figure 4):

1. In darkness, the pupils were almost equal.

2. Dilation in response to psychosensory stimuli was unimpaired on both sides.

3. When the right eye or the left eye was stimulated by light, the right pupil reacted normally, while the contractions of the left pupil were inextensive, sluggish, and preceded by a prolonged latency period. Since the left pupil always showed the pathologic response, regardless of which eye was stimulated, we were dealing with an efferent lesion. Since fatigue of the remnant reflex of the left pupil was not greater than in the normal pupil, the lesion had to be considered postnuclear.[3]

Case 3.—Pupillary syndrome of bilateral alternating contraction anisocoria in a case of encephalitis in early childhood.

The patient was a 10 year old boy who at the age of four had suffered from an acute febrile illness accompanied by somnolence. Two years later he developed a twitch of his eyes and became increasingly nervous. He became

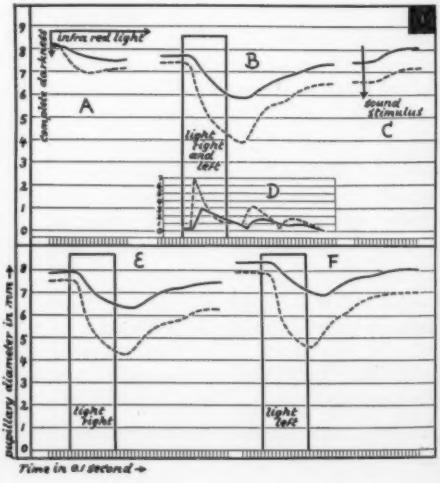

FIG. 4. *Case 2. Damage to the right efferent third nerve in a case of multiple sclerosis.*

The pupillary diameters are plotted (in mm.) against itme (in 0.1 second), the solid line representing the right, the broken line the left pupil. In the differential curve (D), contraction-resp. dilation-speed is plotted (in mm./sec.) against time (in 0.1 second).

A: In complete darkness, the pupils are equal at 8.1 mm.; the dark red-infrared light causes both pupils to contract slightly, the left more than the right. When the right (E), the left (F), or both (B) eyes are exposed to 15 foot-candle light stimuli, the left pupil reacts normally, but the right pupil's contractions are inextensive, sluggish, and preceded by a prolonged latency period. These characteristics can be seen most clearly in the differential curve (D), which shows the low and delayed peaks of all parts of the reflex. The responses to psychosensory stimuli are unimpaired on the two sides.

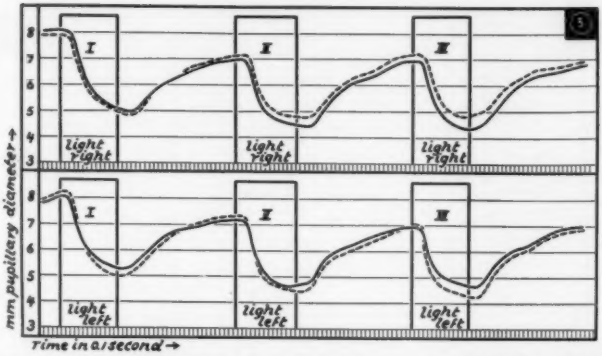

FIG. 5. *Case 3. Bilateral alternating contraction anisocoria in a case of encephalitis in early childhood.*

Pupillary diameter is plotted (in mm.) against time (in 0.1 second), the solid line representing the right, the broken line the left pupil.

The first, second, and third light reflexes of two series are shown. In one series (first line) the right eye is exposed to the stimulating light, while the left eye remains in darkness. In the second series (second line) the left eye is stimulated, the right pupil reacting consensually. In each case, the two pupils do not respond equally; the direct reaction of the stimulated eye is normal, but the consensual reaction of the opposite pupil is slightly slower and less extensive. Consequently, the pupils become unequal during the contraction phase.

aggressive toward other children, extremely disobedient, and could not fall asleep in the evening though he slept for hours during the day. He had spells of hyperventilation which sometimes lasted throughout the night and were accompanied by profuse sweating.

Neurologic examination: The patient was very obese. He showed muscle twitching in both arms and neck and muscle rigidity with incapability of relaxing the upper and lower extremities. Otherwise the reflexes, motor, and sensory functions were unimpaired.

Pupillographic studies: When the eyes were adapted to darkness, the pupils were equal at 8 mm. Extent and shape of the direct light reflexes were within normal limits. However, the two pupils did not respond equally. The consensual response of either pupil was less extensive and slower than the direct response of the opposite pupil, regardless of which eye was stimulated (figure 5). This syndrome of "alternating contraction anisocoria" was shown to be localized in the anterior midbrain.[4] The lesion involves both brachia of the superior colliculi and the posterior commissure, but not the third nerve nucleus or the efferent third nerve fibers.

Case 4.—Bilateral incomplete Argyll Robertson syndrome in a case of syphilis of the central nervous system.

The patient, a 65 year old man, had a long history of syphilis with extensive antiluetic treatment. Twenty-five days before examination he had a fainting spell, followed by dizziness of three days' duration. He gradually recovered his strength, but still suffered from diplopia, blurred vision, and increasing deafness of the right ear.

Physical examination showed a blood pressure of 180/50, a precordial systolic murmur, and a soft diastolic murmur over the aortic area. X-ray examination of the chest showed advanced aortitis, probably syphilitic in origin, and advanced general arteriosclerosis. Cerebrospinal fluid tests and blood tests were negative, but it was reported that blood tests had been positive in the past.

Neurologic examination: The deep reflexes were hyperactive, the gait ataxic; there was a positive organic Romberg phenomenon with swaying to the right side.

Pupillographic studies confirmed the clinical diagnosis of incomplete Argyll Robertson syndrome (figure 6). Both pupils remained small in darkness, the right measuring 4.15 mm., the left 3.75 mm. The reactions to light were inextensive and very sluggish, never exceeding 1 mm. They had the shape of spastic reflex paralysis, with a prolonged latency period, and low, delayed peaks of contraction speed, as

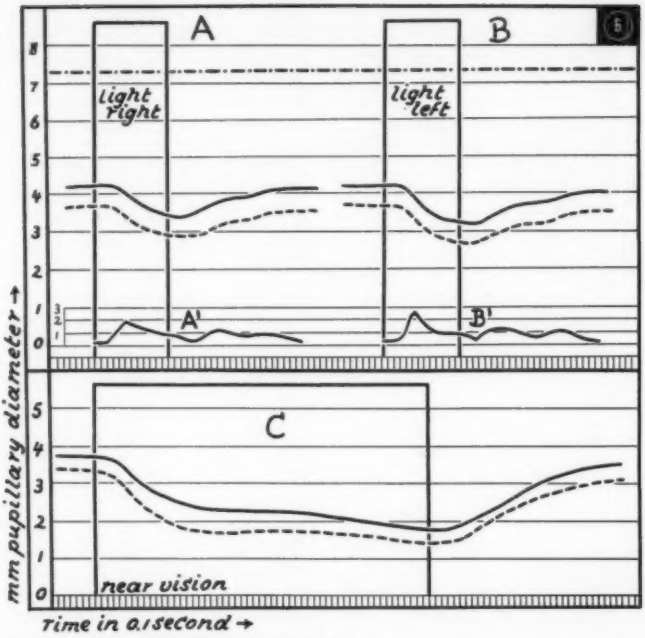

FIG. 6. *Case 4. Incomplete Argyll-Robertson Syndrome.*

Pupillary diameter is plotted (in mm.) against time (in 0.1 second), the solid line representing the right, the broken line the left pupil.

A and B: The dash-dot line represents the normal, dark-adapted pupillary diameter, showing that the pupils in this case are far smaller than normal. When the right (A) or the left (B) eye is exposed to a strong light stimulus, the reflexes are extremely shallow and inextensive. The differential curves A' and B' show the low and delayed peaks of speed of all parts of the reactions.

C: During the reaction to near vision both pupils contract to the limits of mechanical possibility, becoming far smaller than they did during the most extensive contraction to light.

seen in the differential curves (figure 6.-A1 and B1). During the reaction to near vision, both pupils contracted almost to the limits of mechanical possibility, the right pupil contracting to 1.8 mm., the left to 1.5 mm. In contrast to this, the strongest light stimuli failed to contract the pupils to a smaller diameter than 2.75 mm. for the left and 3.1 mm. for the right pupil.

Case 5.—Probable postencephalitic parkinsonism with pupillary reactions of tonohaptic shape.

The patient, a 52 year old woman, had never been seriously ill, but between the ages of 20 and 30 she had suffered from frequent infections, with sore throat, headaches, and elevated temperatures. Eighteen years before examination she first noticed a slight tremor of the head, which became more pronounced under emotional stress. The tremor gradually increased and both upper extremities became involved.

The neurologic examination showed a constant rotating tremor of the head and a fine tremor of the outstretched fingers. The deep reflexes were active, the abdominal reflexes present. There were no pyramidal signs. Her speech was slow but without articulatory disturbances. She showed increased sweating all over the body, a shiny face, and protruding eyes. She was sleepy during the day, but sleepless and restless during the night.

Pupillographic studies: The dark-adapted pupils were equal and small. The reactions to light

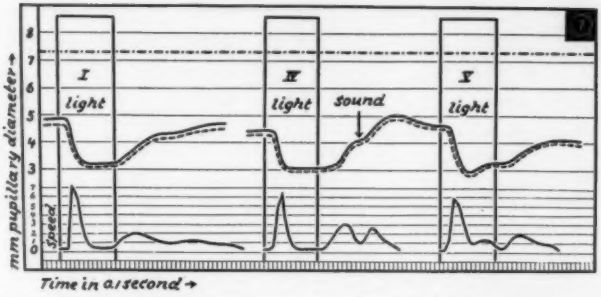

FIG. 7. *Case 5. Tonohaptic pupillary reactions in a case of postencephalitic parkinsonism.*

Pupillary diameter is plotted (in mm.) against time (in 0.1 second), the solid line representing the right, the broken line the left pupil. The first, fourth, and fifth reactions of a continuous series are shown. The dash-dot line represents the diameter of the normal dark-adapted pupil.

The pupils are equal. As in case 4, they are far smaller than normal, the reactions less extensive than normal; but unlike the reactions of case 4, contraction occurs at fast speed, and the latency period is slightly shorter than normal. The entire contraction movement is accomplished within 0.3 second, the pupils then remaining at full contraction until some time after the light stimulus has come to an end. A sound stimulus, interposed between the fourth and fifth light stimuli, causes normal psychosensory dilation but fails to restore the normal shape of the following reflex.

were inextensive but rapid. Tonohaptic light reflexes confirmed the presence of a lesion in the diencephalon. The normal pupillary dilation in response to psychosensory stimuli indicated that the sympathetic centers in the ventral lateral hypothalamus and the efferent sympathetic system through the cervical cord and peripheral sympathetic chain were not involved (figure 7).

Case 6.—Central sympathetic irritation with inhibited light reactions of mydriatic pupils.

The patient, a 21 year old college student, had been a child prodigy, too advanced for his age. He had always been hypersensitive, went through numerous periods of reactive depression, and had difficulties with his classmates and teachers. At the age of 18 he started to suffer from insomnia. He read throughout the night and worked without interruption throughout the day. His excitability increased, with sweating all over the body, increased heart rate up to 150, and frequent profuse diarrhea of long duration.

The neurologic examination showed increased deep tendon reflexes but no other symptoms.

Pupillographic records: (figure 8.-A and A1). The pupils were equal and large. The reactions to light showed all the signs of sympathetic hyperexcitability: they were inextensive and had W- or V-shape throughout. Psychosensory stimulation further exaggerated these characteristics. Although the mydriatic pupils showed a diminished extent of the contraction to light, the parasympathetic reflex arc was unimpaired. This was demonstrated in the differential curves where the light reflexes showed normal peaks of contraction speed. These peaks gradually increased upon repeated light stimulation, as the hyperirritative sympathetic fatigued earlier than the parasympathetic which then could overcome the pathologically increased sympathetic tonus. W-shaped light reflexes, when due to either low intensity light stimulation or to advanced fatigue, show low peaks of contraction speed which decline even further upon repeated stimulation (compare figures 8.-B and 9).

Case 7.—Heredodegenerative condition involving the diencephalon and mesencephalon, with permanent pupillary fatigue reflex shapes.

The patient, a 43 year old man, came from a nervous family. His father suffered from chronic mental depression. His mother was nervous, with a "violent temper." The patient had always had good muscle strength but had felt weak and tired for as long as he could remember. He went through high school and college with great difficulty because he could not concentrate, fell asleep at 8 o'clock in the evening, and after 12 to 14 hours of deep sleep awoke "dead tired." If he went back to sleep, he felt even worse upon awakening later. About 12 years prior to examination, he went through a three month period during which he was "in a daze," without feeling men-

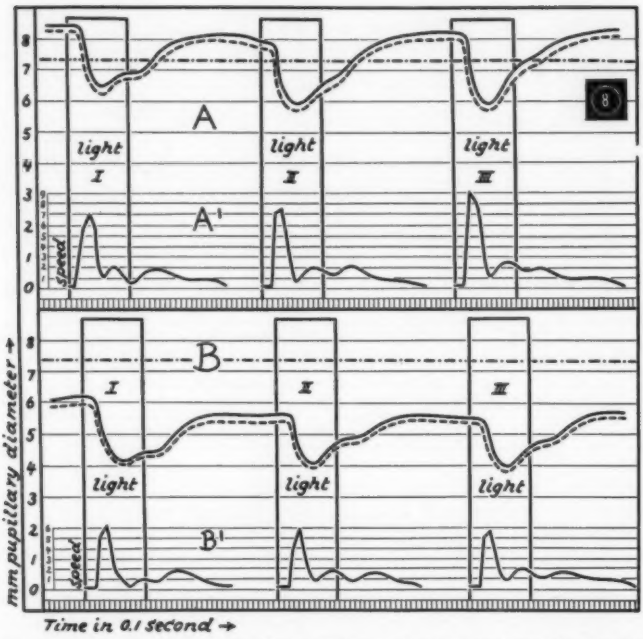

FIG. 8. A: *Case 6. Chronic central sympathetic irritation.* B: *Case 7. Chronic central nervous fatigue.*

Pupillary diameter is plotted (in mm.) against time (in 0.1 second), the right pupil being represented by the solid line, the left pupil by the broken line. The first, second, and third reactions of each series are shown.

In case 6 (A), the pupils are larger; in case 7 (B), they are smaller than normal (note the dash-dot line, representing normal dark-adapted pupillary diameter). In both cases, the reflexes have V- or W-shape.

In case 6 (A), the parasympathetic reflex arc is unimpaired, as shown by the normal latency period and normal peak of contraction speed. As soon as the peak of contraction force has been passed, the powerful sympathetic antagonist interrupts the contraction movement and forces the pupils to redilate prematurely. It can be seen that the peak of contraction speed (A') increases from reaction to reaction, as the abnormal sympathetic tonus is depressed by repeated parasympathetic stimulation.

In case 7 (B), a similar equilibrium between sympathetic and parasympathetic impulses causes similar reflex shapes, but in this case, both factors are weak. The latency period for contraction is slightly increased, the peak speed of contraction is lower than normal, and declines from reaction to reaction (B').

tally depressed. His blood pressure had always been low, but the systolic blood pressure was never found to be below 100 mm. Hg.

The neurologic examination was completelv negative. Electrocardiogram, electroencephalogram, spinal fluid, blood sedimentation rate, blood serology, and temperature were normal. The blood pressure was 120/80. The basal metabolism, taken at various times, was normal. Excessive sweating was observed all over the body.

The pupillographic records (figure 8.-B) revealed pupils of smaller than normal size which responded to light stimuli with inextensive W- and V-shapes. Such pupillary light reflexes are found in normal subjects with advanced fatigue; but in contrast to normal subjects, psychosensory stimuli failed to restore the normal pupillary reflex shape, that is, the psychosensory restitution phenomenon was absent. Such permanent and irreversible fatigue patterns are indicative of an organic disorder of the central

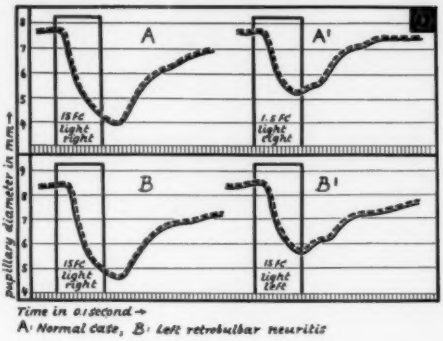

FIG. 9. *Case 8. Unilateral lesion of the optic nerve in a case of retrobulbar neuritis.*

Pupillary diameter is plotted (in mm.) against time (in 0.1 second), the solid line representing the right, the broken line the left pupil. *A and A'*: Pupillary reactions of a normal subject (for comparison). In A, the right eye is exposed to a light stimulus of 15 foot-candle intensity. In A', the same eye is stimulated by a weak (1.5 foot-candle) light. This stimulus elicits an inextensive, W-shaped response. The contraction speed is slower, the latency period longer than in A. *B and B'*: Pupillogram of case 8. In B, the right eye, and in B' the left eye is exposed to the same 15 foot-candle light stimulus, the other eye remaining in darkness. When the right eye is stimulated, both pupils react normally, but when the left eye is stimulated, a low intensity reflex is produced. Note the absence of anisocoria.

nervous system involving diencephalic and midbrain structures. In this case, the condition was probably heredodegenerative in nature.

Case 8.—Pupillary reactions to light of "low intensity" shape in a case of multiple sclerosis with seemingly cured retrobulbar neuritis.

The patient, a 39 year old man, developed diplopia and blurred vision in the left eye in January 1954. He recovered within a day or two without having seen a physician. In July 1954 the symptoms recurred.

Upon examination vision in the left eye was reduced to counting fingers at one foot. Papilledema existed in the left eye. The general neurologic examination showed diminished abdominal reflexes on the left side, but no other signs.

A few days later his vision had returned to 20/20, and the diplopia had disappeared. A diagnosis of multiple sclerosis was made.

When the patient was seen in October 1954, he complained of general nervousness, insomnia, and increased excitability. The neurologic examination showed increased deep reflexes but no other signs of involvement of the central nervous system. Abdominal and cremasteric reflexes were normal on both sides. The fundi of both eyes and vision were normal.

Pupillographic studies (figure 9): The pupils were equal both in light and in darkness. When the right eye was stimulated by light of 15 foot-candle intensity, the pupils reacted normally. But when the left eye was stimulated by the same intensity light, the reaction of both pupils was inextensive and showed W- or V-shapes. The contraction speed was slower than normal, the latency period slightly prolonged. This type of reaction resulted from stimulation of the normal right eye only when low intensity light (1.5 foot-candle) was used.

V- or W-reflex shapes appear in response to low intensity light stimuli, because the parasympathetic stimulation is weak, while the sympathetic antagonist is normal and therefore relatively strong. The low intensity reflex shape elicited from the left eye indicated the continued presence of a lesion in the afferent path of the light reflex arc, anterior to the optic chiasm. It should be noted that, contrary to widely held opinion, uncomplicated lesions of the afferent light reflex path anterior to the pretectal area, do not result in anisocoria.[5]

CONCLUSIONS

Pupillary disturbances as found in diseases of the central nervous system lead to a large variety of deviations from the normal reflex pattern. These abnormalities, when graphically recorded, show a great variety of reflex shapes which escape observation by the unaided eye but are distinctly characteristic in pupillographic records. Each indicates damage at a specific site within the centers and pathways of pupillary control. Therein lies their value for topical diagnosis.

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■ The fact that the loss of sensibility seems to be absolutely complete, after a longitudinal section of the whole length of the lumbar enlargement of the spinal cord seems to show that all the conductors of sensitive impressions which reach the cord, coming from the posterior limbs, make their decussation in this enlargement. But if we admit that the decussation is complete, how do we explain that there is an appearance of sensibility, and sometimes a well-marked degree of it, in a limb on the opposite side to that of a section of a lateral half of the spinal cord? In the first place, I must say that very often when we try to divide transversely such a part of the cord, being afraid of cutting too much, we leave undivided a part of the gray matter and of the anterior column, so that the persistence of sensibility in the opposite side of the body is very natural, and not in opposition to our views. Very likely this is what has occurred in many of the experiments of Mr. Chauveau, who says that sensibility always persists in such a limb. If there is no notable diminution of sensibility anywhere, after an attempt to divide the lateral half of the cord, it is certain that the operation is not complete, and that a part has escaped division. It is wonderful how small is the quantity of gray matter, which, being left undivided, may transmit sensitive impressions!

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Vomiting: Neural Mechanisms and Control by Chlorpromazine

William Amols, M.D. and H. Houston Merritt, M.D.

VOMITING, LIKE PAIN, is a frequently encountered symptom of disease, distressing to the patient and challenging to the physician. Yet, unlike pain, the pharmaceutical armamentarium available to cope with it has, until recently, been sparse and inadequate. The advent of chlorpromazine (10-(5-dimethylaminopropyl)-2-chlorphenothiazine hydrochloride) raises the hope of providing to the practitioner a drug of known pharmacologic activity which will be as specific for the control of vomiting as morphine has been for pain.

Despite the frequency of vomiting as a symptom, little attention has been given to the mechanisms involved except in the specialized journals of physiology and pharmacology. It is the purpose of this paper to describe current concepts of the vomiting act, to review the physiologic background of these concepts, to present the clinical evidence of the antiemetic properties of chlorpromazine, and to review the experimental data in regard to the method of action of this drug.

Vomiting is a complex coordinated defense mechanism which is principally a function of the respiratory and not the gastrointestinal system. It is the means by which the contents of the stomach and upper intestinal tract are forcibly emptied through the mouth, but in which both these structures seem to play a passive role. Indeed, vomiting has been experimentally induced in animals not only after total gut denervation, but after abdominal evisceration as well.[1] One of the earliest and most graphic descriptions of the minor role of the stomach and intestine in vomiting is that of Cannon.[2] He observed the movements of the cat's stomach following a bismuth meal and the administration of apomorphine. The stomach was described as a flaccid bag sharply demarcated at its lower end by a ring of constriction and completely without tone at its upper end. The stomach contents were then forcibly ejected through the open cardia into the esophagus by the strong compression exerted by sharp contractions of the diaphragm and ab-

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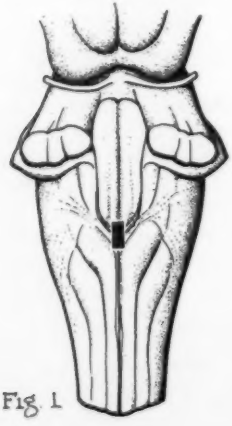
dominal muscles. The esophagus remained relaxed, the glottis closed, the larynx and hyoid bone drawn forward, the soft palate elevated, and normal respirations were inhibited.

In addition to these coordinated muscular phenomena, certain other concomitants of the vomiting act have long been recognized. These include salivation, forced inspiration, vasomotor changes, characteristic postures, and psychic phenomena. The complexity with which each component is coordinated with the others led Giannuzzi,[3] as early as 1865, to postulate a center for vomiting within the nervous system. The first attempt at localizing such a center was that of Thumas[4] in 1891. He found that vomiting could be induced in dogs by the application of apomorphine to the caudal end of the floor of the fourth ventricle, and that this response to apomorphine could be abolished by ablating this area. He concluded that the vomiting center resided in the medulla oblongata in a midline area 2 mm. wide and 5 mm. long which extended through the obex (figure 1).

In 1923 Hatcher and Weiss[5] repeated Thumas' work but found that, although ablation of the area described rendered the animal unresponsive to apomorphine, vomiting could still be induced by the oral administration of mercuric chloride. By producing lesions in the ala cinerea bilaterally (figure 2), they were able to abolish vomiting to both apomorphine and mercuric chloride. They considered that their lesions had destroyed the true vomiting center and that Thumas had inadvertently damaged the adjacent ala cinerea when making his midline lesion. Their conclusions were based on acute experiments in animals. In 1930 Koppanyi,[6] using animals with chronic lesions in the ala cinerea, found that although their sensitivity to parenteral apomorphine was greatly reduced, they still vomited readily to orally administered irritant emetics. While he attributed this selective response to incomplete destruction of the vomiting center, the earlier conclusion of Hatcher and Weiss that the location of this center resided in the ala cinerea became less valid.



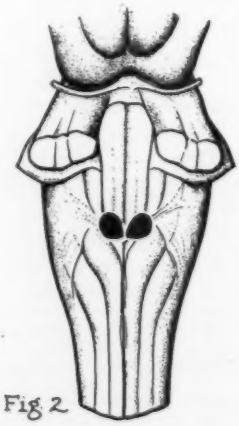


FIG. 1. Ablation of midline structures at level of obex, rendering dog refractory to topical apomorphine (Thumas, 1891). Hatcher and Weiss in 1923 confirmed Thumas' results, but obtained vomiting with intragastric mercuric chloride.

FIG. 2. Bilateral superficial lesions in ala cinerea in acute animals abolished emesis to apomorphine and irritant emetics (Hatcher and Weiss, 1927). Identical lesions in chronic animals abolished emesis to apomorphine but not to irritant emetics (Koppanyi, 1930).

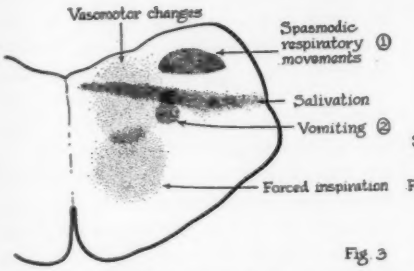


Fig. 3

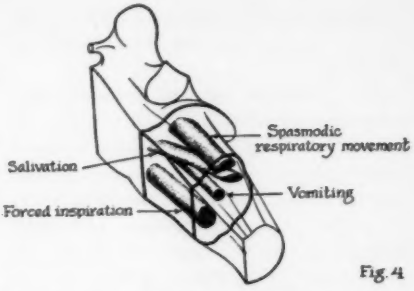


Fig. 4

FIG. 3. In anesthetized animals, Borison (1948) obtained spasmodic respiratory movements, but no vomiting. In decerebrate animals, Borison and Wang (1949) obtained true vomiting.
FIG. 4. Phantom drawing of lower brainstem showing areas from which vomiting and its individual components were obtained.

Little was accomplished to clarify the problem of localization until 1948 when Borison[7] followed up an observation reported by Wang and Ranson[8] that an unusual augmented respiratory response was elicited on electrical stimulation of the cat's brainstem at the level of the calamus scriptorius. Working with Nembutal-anesthetized cats and using the Horsley-Clarke stereotaxic instrument for exact localization, he obtained a spasmodic respiratory response which he recognized as similar to that which occurs in coughing, sneezing, and retching. This suggested to him that one component of the vomiting complex had independently been obtained, and prompted him to search for the other individual modalities. The area from which he elicited this response was in the dorsolateral region of the medulla oblongata (figure 3).

In 1949 Borison and Wang,[9] using decerebrate cats because anesthesia is known to depress the vomiting response, stimulated the medulla through bipolar electrodes and succeeded in eliciting individually the various component elements of vomiting, that is, salivation, spasmodic respiratory movements, forced inspiration, and vasomotor responses. One or more of these responses were obtained from various and relatively widespread regions of the medulla (figures 3 and 4), but the complete, coordinated act of vomiting was consistently obtained by stimulation of one specific point. On sectioning, this point proved to be located at the dorsolateral border of the lateral reticular formation in the region of the fasciculus solitarius and its nucleus. Salivation, nose-licking, and swallowing – interpreted as indicating nausea – were occasionally observed from this region when vomiting did not occur. Stimulation in the ala cinerea in the area believed by Hatcher and Weiss to be the site of the vomiting center failed to produce emesis.

The discovery of this area, which on stimulation produced the complicated vomiting act in its entirety, and which resided so close to the region from which so many of the components of vomiting could be individually elicited, prompted the idea that it might represent the true vomiting center – not in the old sense that it carried out the act of vomiting, but rather that it consisted of a neural pool for coordinating the activities of

other neural structures in its immediate vicinity to produce the total patterned response.

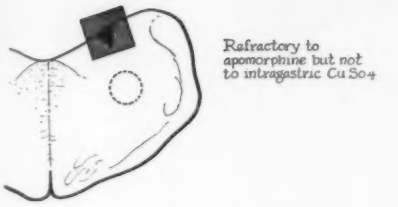
Two problems now interposed themselves for solution: 1) What was the relationship of this area to the more superficially placed region in the ala cinerea, destruction of which abolished the emetic response to apomorphine? 2) Would destruction of this area eliminate the usual response to emetic drugs?

The following year Wang and Borison[10] sought to destroy this area by means of a cold cautery inserted into the region through the floor of the fourth ventricle, just as they had done in their stimulation experiments. Not all attempts were successful, but it was noted after sectioning the brains that when the lesion produced was superficial, that is, too shallow to reach the supposed vomiting center, the animals were refractory to apomorphine but not to orally administered copper sulfate, an irritant emetic. When the lesion was deep enough to destroy the vomiting center as well as the superficial area, the animals were refractory to both agents (figure 5). These observations suggested that there was a different site of action for each of the two drugs: apomorphine acting on the superficial area, and copper sulfate on the deeper one. But the question of what would happen if the deeply placed "vomiting center" were selectively destroyed while sparing the superficial area was not yet answered. In addition, it now became desirable to discover by what means copper sulfate acts as an emetic.

In 1951 these same investigators[11] showed that in dogs with total denervation of the gut, intragastric copper sulfate in large quantities was ineffective as an emetic agent until a latent period of about two hours had passed, in contrast to the short (12 minutes) latency in the normal dog. In both normal and gut-denervated dogs intravenous copper sulfate produced prompt emesis. Ablation of the superficially placed area in the ala cinerea* abolished both the delayed emesis following intragastric administration in the gut-denervated preparation and the immediate emesis from intravenous copper sulfate. From this they concluded that copper sulfate causes emesis in the intact animal by reflex stimulation of the center via the vagal and sympathetic afferents, but that if vomiting is prevented from occurring by total gut denervation, enough copper sulfate may be absorbed into the blood stream to act as a "central" emetic by stimulating the superficially located chemosensitive area in the ala cinerea, which in turn activates the more deeply placed vomiting center. Because of its demonstrated sensitivity to circulating drugs and its ability to activate the vomiting center, Wang and Borison named this superficial area the "chemoceptive emetic trigger zone."

Later the same year (1951), these investigators[12] were able to achieve their second objective: that of selectively destroying the deeply placed vomiting center while leaving the more superficial chemoceptive emetic trigger zone intact. This was accomplished by means of the insertion of tiny glass and gold radon seeds of calculated dosage through a hollow needle via the cervical flexure of the cord in dogs (figure 6). With this technic it was possible in a significant number of instances to destroy by radiation the immediate vicinity of the deeply placed vomiting center while leaving ad-

*Actually found to be located lateral to the ala cinerea in the area postrema.[25,27]



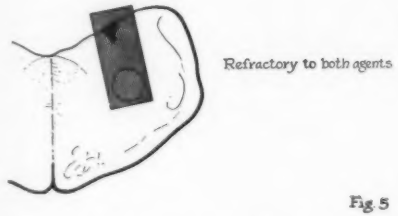
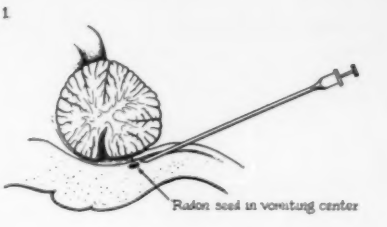


Fig 5



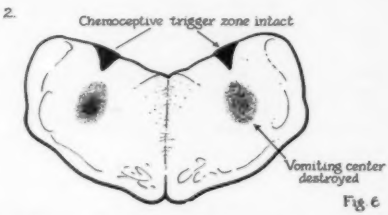


Fig 6

FIG. 5. Relative refractoriness to various emetic agents by destruction of the superficial area alone and the combined superficial and deep areas (Wang and Borison, 1950).

FIG. 6. 1. Technic of implantation of radon seeds in vomiting center (Wang and Borison, 1951). 2. Selective destruction of vomiting center sparing chemoceptive trigger zone, producing refractoriness to both apomorphine and intragastric copper sulfate.

jacent structures intact. As anticipated, these animals showed appreciable and significant elevations of their thresholds to both apomorphine and copper sulfate, proportional to the extent and accuracy of the lesion.

Thus the older unitary hypothesis of the vomiting center has been replaced by a new concept of the organization of the central emetic mechanism, as consisting of a neural pool in the lateral reticular formation which coordinates the various components of the vomiting act, and which can be activated by two mechanisms: 1) the nearby chemoceptive emetic trigger zone in the highly vascular area postrama, and 2) the vagal and sympathetic afferents from the gut. The chemoceptive emetic trigger zone is sensitive to drugs and other agents with a so-called central emetic action, while the visceral afferents mediate the effects of irritant emetics (figure 7).

With this knowledge of the neural mechanisms of vomiting, it is theoretically possible to discover at what point and by what means an antiemetic agent acts. Within the past three years convincing data has accumulated in the literature that chlorpromazine is an effective antiemetic agent. Its ability to prevent apomorphine-induced emesis in animals was reported by Courvoisier and associates in 1953[13] and by Boyd and coworkers in 1954.[14] Cook and Toner reported it to be effective against swing-induced emesis in dogs.[15] A number of clinical investigators have found the drug beneficial in human patients with nausea and vomiting from a variety of causes.[16–20] We studied the efficacy of chlorpromazine as an antiemetic in 50 patients with vomiting from a variety of causes including increased intracranial

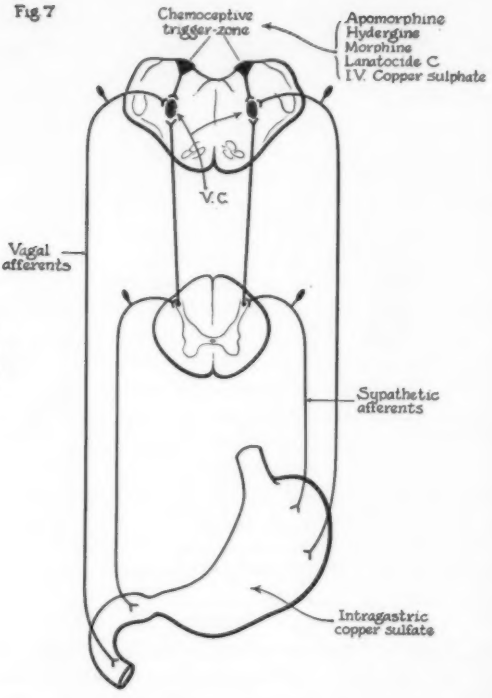


FIG. 7. Current scheme of vomiting mechanism showing agents known to act at chemoreceptive trigger zone and reflexly via autonomic afferents.

pressure. The effective dose varied from as little as 25 mg. intramuscularly to as much as 300 mg. by mouth in divided doses over 24 hours. The favorable results of our study (table 1) are similar to those reported elsewhere.[16–20] These encouraging clinical reports stimulated further interest in the pharmacodynamics of chlorpromazine.

Certain emetic agents have been shown by appropriate ablation studies to have as their site of action the chemoceptive emetic trigger zone. These include apomorphine,[21] morphine,[22] and intravenous copper sulfate.[21] Certain others, principally intragastric copper sulfate, are known to cause vomiting by their irritant action on the gut mediated directly to the reticular vomiting center via the visceral afferents[23] (figure 7). When dogs were premedicated with chlorpromazine in doses ranging from 1.5 mg./kg. to 3.0 mg./kg. subcutaneously, dramatic protection was obtained against the vomiting invariably caused by apomorphine and Hydergine given intravenously (their thresholds were raised roughly ten times).[24,25] On the other hand only negligible protection was afforded against intramuscular morphine and no protection against intravenous lanatocide C or copper sulfate.[25] By increasing the dose of chlorpromazine to 4 mg./kg., a 43 per cent degree of protection against intramuscular morphine could be obtained, but none to lanato-

TABLE 1
RESULTS OF THE USE OF CHLORPROMAZINE IN THE CONTROL OF VOMITING (50 CASES)

Causes of vomiting	*Number of cases*	*Vomiting eliminated*	*Improved*	*Not helped*
Brain tumor	14	10	4	
Cerebral vascular accident	3	3		
Subarachnoid hemorrhage	2	2		
Carcinomatosis	12	7	3	2
Uremia	4	4		
Intestinal obstruction	3	1	2	
Gastroenteritis	1	1		
Postoperative	4	2	1	1
Ménière's syndrome	1	1		
Pregnancy	1	1		
Amyloidosis	1	1		
Psychological	1			1
Demerol	2	2		
Nitrogen mustard	1	1		
Totals	50	36	10	4
Per cent	100	72	20	8

cide C or copper sulfate. Yet all those animals who were protected against these central emetics could still be made to vomit by threshold doses of intragastric copper sulfate.[25]

These results suggest that chlorpromazine in these doses has as its site of action the chemoceptive emetic trigger zone. But the observation that some of the central emetic agents are easily inhibited by relatively low doses, while another is only partly neutralized by higher doses, and still others are not affected at all, has caused considerable speculation on the mode of action of chlorpromazine at this site. It has been suggested[25] that there is a receptor substance at the chemoceptive emetic trigger zone which has an affinity for the centrally active emetic agents and for chlorpromazine as well. In certain cases (apomorphine, Hydergine), chlorpromazine may be a more effective competitor for this receptor substance. In others (morphine) it is less so, or not at all (lanatocide C, intravenous copper sulfate).

When chlorpromazine was administered intravenously in doses as high as 6 mg./kg., not only was its protective effect against apomorphine, Hydergine, and morphine more pronounced, but it now prevented vomiting from intragastric copper sulfate as well.[25] Since the immediate action of the latter agent is on the reticular vomiting center via the visceral afferents, without involving the chemoceptive emetic trigger zone, a second site and action of chlorpromazine must be postulated, namely that of directly depressing the reticular vomiting center itself when given in large doses intravenously.

This dual action of chlorpromazine may explain, to some extent, the published observations of its usefulness as an antiemetic agent in man in such a wide variety of conditions causing nau-

sea and vomiting. These include drug toxicity, infections, intoxications, neoplasms, radiation sickness, cardiovascular diseases, increased intracranial pressure, and gastrointestinal disorders including acute gastritis and intestinal obstruction. Were the drug to have only an effect on emesis of central origin these latter two conditions might not be expected to respond. That they do respond may be further evidence of the ability of chlorpromazine to depress the vomiting center.

SUMMARY

1. Vomiting is primarily a function of the respiratory and not of the gastrointestinal system.

2. Vomiting is controlled by a neural mechanism consisting of a superficial area (chemoceptive trigger zone) located in the area postrama in the fourth ventricle and a coordinating center in the lateral reticular formation of the medulla oblongata. The chemoceptive trigger zone is composed of specialized cells which are sensitive to circulating chemical agents, and, when properly stimulated, activates the more deeply placed reticular vomiting center. The latter may also be activated directly by visceral afferents from the gut.

3. Chlorpromazine, a clinically effective antiemetic, has been found to act on both of these areas. In small doses it is believed to compete with circulating emetic agents for receptors in the chemoceptive trigger zone, thus acting as a competitive inhibitor. In larger doses it has been shown to have a depressant effect directly on the reticular vomiting center itself.

Chlorpromazine supplied under trade name "Thorazine" Hydrochloride by the Smith, Kline, and French Laboratories, Philadelphia.

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■ The question relative to the place of passage in the spinal cord, of the impressions of temperature, and of some other kinds of impressions, cannot be solved positively by vivisections. We can say, however, that after a transverse section of the whole spinal cord, except the posterior columns, in the dorsal region, the application of ice or of fire to the toes seems not to be felt, and that also spasm may be induced in the muscles of the paralyzed legs without causing a sensation. It seems, therefore, that the posterior columns are not the channels of transmission of these impressions.

Some experiments also seem to show that the conductors of these impressions decussate in the spinal cord. But pathological facts observed in man will teach us much more concerning all the sensitive impressions which are not purely painful, than experiments upon animals. In consequence, we shall postpone also till we come to pathological facts, what relates to this question: Is it possible to recognize the place upon which an impression is made, when the posterior columns of the spinal cord are divided or altered? We will merely say, at present, that animals, after a section of the posterior columns or of a lateral half of the spinal cord, seem to discover the point irritated, as although their eyes are covered, they try to bite near the place upon which a painful irritation has been produced.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Spontaneous Bilateral Labyrinthine Deficit

Joe R. Brown, M.D.

LITTLE ATTENTION has been paid in textbooks of neurology or otolaryngology to symptoms of bilateral deficiency of vestibular sensation. At least one reason for this fact is that many patients compensate reasonably well to labyrinthine deficiency. Ford [1] described unsteady gait and difficulty in visual fixation when the head is in motion as occurring after section of the vestibular portion of the eighth cranial nerve. He stated that these conditions persisted for three months after section of one nerve but were prolonged and "probably permanent" following bilateral section of the vestibular nerve. Brown and Hinshaw[2] described similar symptoms following the use of streptomycin in the treatment of tuberculosis. The labyrinths of their patients showed reduced response or absence of response to the turning and caloric tests for labyrinthine function. Some patients showed slight response to caloric stimulation when the turning test did not elicit any response. Compensation for loss of labyrinthine function took place in two to four months and was fairly complete. The time required for compensation varied and the adaptation was better among the younger patients.

Compensation for loss of labyrinthine function is considered to occur by utilization of proprioceptive, visual, and tactile stimuli. It is conceivable that some vestibular sensation may remain, even in the absence of demonstrable response to the caloric test. It is apparent from the description by Ford[1] that bilateral deficit of vestibular sensation may leave symptoms which are apparently permanent. The author has recently seen three patients with complaints of unsteadiness of gait, particularly in the dark. They also complained of a sense of objects moving when their heads or bodies were in motion. The symptoms came on spontaneously without obvious cause and were persistent and unremitting. The only abnormal neurologic findings were unsteady gait and the absence of response of both labyrinths to caloric and rotational stimulation.

REPORT OF CASES

Case 1.—A 37 year old dentist registered at the Mayo Clinic in February 1953. His chief

From the section of neurology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

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complaints were unsteadiness of gait and difficulty with vision. He had not had any serious illnesses previously and the family history was not remarkable. In addition to his chief complaints he had indigestion and abdominal distress of two years' duration.

The patient recalled having had a brief episode of vertigo ten or 12 years previously and a similar episode two years before coming to the clinic. After this second episode of vertigo, unsteadiness and unsureness of gait developed and gradually progressed, as did difficulty with vision. The patient stated that when he walked he had a feeling of insecurity about where he was putting his feet and felt as if he were walking in a rowboat. It was necessary, therefore, for him to watch the ground in front of him. He noticed that as he walked he tended to sway and to bump into doorways. He felt more secure while walking along a wall. Concerning his vision, he stated that relatively distant objects seemed to move up, down, or sideways. After looking at moderately distant objects for a while they seemed to move so that he no longer focused on them. While reading, the print seemed to move. The apparent motion of the objects was accentuated when the patient was walking, and further increased when he was running or riding in a car. It was less noticeable when he was sitting and at such times the movements seemed synchronous with the heartbeat. These symptoms were intensified on lateral gaze.

During the year previous to his registration the patient had noted a continuous high-pitched hum in both ears, but his hearing had not diminished. He did note, however, that sudden loud noises were painful to his ears and were accompanied by a sudden increase in the sense of motion of objects. He stated that he did not feel tense or nervous, but felt some fatigue at the end of a busy day.

The general medical examination did not reveal any abnormality. The ocular fundi were normal. Results of the original neurologic examination were negative except for the slight unsteadiness of gait and positive Romberg's sign. On further neurologic observation certain minor abnormalities were noted. When the patient followed a moving object with his eyes, the globes moved in a jerky manner rather than smoothly. On a few occasions there was a definite horizontal and a slight rotatory nystagmus on the extremes of lateral gaze. Prolonged lateral fixation made the patient feel vertiginous. He staggered markedly when he tried to walk with his eyes closed. He was asked to kneel on a table and close his eyes. When the table was tilted quickly, anteropulsion and retropulsion were so great that he almost fell off. This did not occur if he was permitted to have his eyes open. Examination of the external ear, nose, and throat gave negative results. The audiograms showed completely normal hearing. The caloric test of the right labyrinth did not elicit any response to 30 cc. of ice water. On the left there was only a slight response with 15 cc. of ice water. This established the almost complete absence of vestibular function to caloric stimulation.

Special evaluation of optokinetic reflexes failed to show any primary defect of those mechanisms. Testing with the binocular visual space orientation apparatus gave normal values. When the patient sat in a dark room and looked at a fixed point of light, he stated that the apparent movement of the light was minor. When he stood unsupported and without touching a wall, however, the apparent movements became violent, seeming to jump a distance of three feet when the light was 20 feet away. In a darkened room microscopic observation of the blood vessels of the sclera, while the patient fixed his sight on a small target, showed actual eye movements which were associated with the subjective sense of movement of the object.

The laboratory tests included urinalysis with analysis for lead, arsenic, and porphyrins; determination of hemoglobin; number of leukocytes; concentration of blood sugar, and flocculation test for syphilis; the results of all tests were negative or normal. Roentgenograms of the thorax and gallbladder did not show evidence of any abnormality; those of the stomach showed evidence of a duodenal ulcer, and those of the head showed a shadow indicative of a tiny deposit of calcium located anterior to the pineal body in what was considered to be the habenular nucleus. The electroencephalogram was normal.

Further inquiry into the patient's symptoms gave additional information concerning his disability. He had to lean against his dental chair to maintain a steady stance at work. While hunting he had considerable difficulty aiming the gun at ducks in flight unless he could get his bearings by keeping an object such as a

hunting companion, a tree, or rushes in his peripheral field of vision. Similarly, while fishing, the sudden movement of his body while casting interfered with his ability to cast accurately. On one occasion while swimming he lost his bearings and almost drowned. Once while standing in the rolling surf he almost lost knowledge of his position in space because of the moving water. He had to turn quickly to see land in order to reorient himself. Because of the sense of abnormal movement of objects he had stopped driving a car.

A progressive isolated defect of both vestibular labyrinths developed spontaneously. The patient had not been able to compensate for the bilateral loss of labyrinthine function. His symptoms had limited his activities considerably.

In February 1955 the patient reported by letter that his symptoms continued unabated and that he had had two minor episodes of vertigo. He further stated that he had learned better how to adapt his life to his disability.

Case 2.—A 39 year old welder registered at the Mayo Clinic in July 1954 with complaints of lightheadedness, staggering, and visual difficulty of 18 months' duration. His family history was not contributory. He stated that he had had rheumatic fever at the age of 24 years and a spontaneous pneumothorax at the age of 26.

The present illness began in January 1953 after a persistent head cold. He had not taken any streptomycin. He had had one "shot" of penicillin and had taken 40 grains of acetylsalicylic acid (eight aspirin tablets) daily for three weeks. One week later he suddenly felt unsteady and staggered to either side, backward, or forward when trying to walk. The symptoms increased for a few days and remained constant thereafter. The staggering consisted of an unsteady misstep which occurred every 15 or 20 yards. At the time of the misstep the patient experienced a sensation of freedom in space. His head felt full, as if his ears were filled with water. He complained that his eyes bothered him and said that all objects at which he gazed seemed to have fuzzy outlines. During the 18 months of his illness he had six episodes of vomiting. Because of his unsteady gait and visual symptoms, he was unable to work as a welder and remained unemployed.

Results of the general medical examination were normal except for the patient's obesity. On neurologic examination it was noted that the gait was slightly unsteady; when the patient closed his eyes his gait was markedly unsteady. Evidence of Romberg's sign was positive. The patient did not show anteropulsion or retropulsion if tilted while on his hands and knees with his eyes closed. External examination of the ears, nose, and throat showed them to be normal. The audiogram showed a very mild reduction of hearing for high tones. Neither ear responded to the turning test or to 30 cc. of ice water. As far as could be determined by these tests the vestibular labyrinths were functionless.

Laboratory tests including urinalysis, determination of hemoglobin, leukocyte count, and flocculation test for syphilis gave negative or normal results. Roentgenograms of the head and thorax did not show evidence of abnormality.

This patient was less capable of giving a detailed description of his symptoms than the patient in case 1. The general pattern, however, was similar, and the primary finding was that of bilateral labyrinthine deficit. The only known factors which might have played a role were the head cold and the use of eight aspirin tablets daily for three weeks. The single dose of penicillin given four weeks before the onset of symptoms probably did not play a role in his condition. As in case 1, the etiology is undetermined.

Case 3.—A 52 year old store owner registered at the Mayo Clinic in January 1955 with the main complaint of loss of equilibrium of four years' duration. The family history elicited the information that the patient's mother had severe headaches. The patient had had severe headaches periodically throughout his life; however, they had decreased in frequency and severity in recent years. Five years before his registration he had had weakness in the right shoulder which cleared spontaneously in six months.

The present illness began in 1951 when he suddenly had a sensation of the room spinning for a few seconds. This sensation had recurred four or five times since; each time the episode was very brief. His gait had been unsteady continuously since the first episode and he had had trouble in focusing his eyes when

he was walking. He also had a sense of loss of balance, particularly in the dark.

The results of general medical examination were negative. The ocular fundi were normal. The patient walked with a wide base and was unsteady at the turns. The test for Romberg's sign was negative, as were the results of the rest of the neurologic examination. The external examination of the ears, nose, and throat gave negative results. The audiogram showed moderate loss of hearing of high tones in the right ear. The vestibular labyrinths were unresponsive to the turning test and to 30 cc. of ice water.

Laboratory tests including urinalysis, determination of hemoglobin, number of erythrocytes and leukocytes, and flocculation test for syphilis gave negative or normal results. Roentgenograms of the head and thorax were negative.

The patient recalled that he had had several colds before the onset of his symptoms. He had had six or eight "shots" for the colds. As far as could be determined, he probably did not receive streptomycin.

This patient presented a syndrome similar to that of the other two patients. However, it was less severe and less incapacitating.

COMMENT

The chief purpose of this paper is to call attention to the complaints of patients with bilateral deficit of labyrinthine function. It seems appropriate, however, to review briefly various opinions as to the pathogenesis of such symptoms.

According to Williams,[3] Ménière, in describing the disorder which bears his name, stated that the patient feels, and is, unsteady while walking, or may complain of to-and-fro or up-and-down motion as if on a ship. One of the characteristic findings in Ménière's disease is hypoactive response to caloric testing.[3]

Ménière's disease is considered to be due to changes in the end-organ.[4] Williams discussed Ménière's disease without cochlear symptoms and without vertigo. These two groups made up 10 per cent of 500 cases of Ménière's disease. Vertigo without cochlear symptoms also has been called pseudo-Ménière's disease. These statements seem to reflect the opinion that the symptoms described may arise as the result of disease of the end-organs and that the cochlea may be spared while the labyrinth alone is involved. The vestibular deficit from streptomycin toxicity, however, has been associated with degenerative changes in the vestibular nuclei in the medulla.[5] Dix and Hallpike[4] reviewed 100 cases of vertigo without auditory symptoms. They considered the syndrome to be due to neuronitis of the vestibular nerve, arriving at this conclusion on clinical grounds. In seven of their cases there was complete bilateral loss of vestibular function. These cases would be comparable to the three reported in this paper. Dix and Hallpike emphasized the role of upper respiratory infections in the production of symptoms in their patients and stated that recovery generally occurred within the course of a few years.

In addition to Ménière's disease Williams[3] listed hemorrhage, vascular thrombosis, suppurative otitis, trauma to the head, multiple sclerosis, toxic vertigo, tumors, platybasia, and a number of other conditions as causes of vertigo. A recent textbook on clinical neurology[5] listed in its index some 29 causes of vertigo. Many of these may cause unilateral or even bilateral reduction of response to the caloric tests. It would seem probable, therefore, that the syndrome discussed in this paper may be due to a number of different pathologic processes which may act on the end-organ, the vestibular nerve, or the vestibular nuclei.

SUMMARY

Case reports of three patients with symptoms of bilateral labyrinthine deficit showed that symptoms came on spontaneously without known specific cause. Two of the patients had had head colds preceding their symptoms and had received medication. The amount of medication received ordinarily would not be expected to produce the symptoms which these patients had. The complaints included unsteady gait and difficulty with visual fixation. The unsteadiness of gait increased in the dark and the visual symptoms increased with motion of the body. The only definite findings were unsteady gait and bilateral unresponsiveness of the vestibular labyrinths. Description of symptoms and findings are given in considerable detail in case 1.

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■ Another cause of error committed by some experimenters was in thinking that the absence of sensibility in the gray matter of the spinal cord is a proof that this matter is not a conductor of the sensitive impressions. A distinction between the property of conduction or transmission, and the property of being sensitive or impressionable, would have presented such a mistake. The nerve-fibres of the cerebral lobes are conductors, but they are not excitable, not impressionable; and so is the gray matter of the spinal cord; when it exists alone, establishing the communication between two parts of the spinal cord, after a transversal section of the whole of the white matter, it conducts, it transmits to the brain the sensitive impressions made on impressionable organs behind the section, but when irritated it does not transmit anything because it is not itself impressionable.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

CLINICAL PATHOLOGIC CONFERENCE

E. P. Richardson, Jr., M.D. Section Editor

Presented by *Philip R. Dodge, M.D. and Bertram E. Sprofkin, M.D.*

PRESENTATION OF CASE

A 29 year old Negro man was admitted to the contagious disease ward of the United States Army Hospital, Ft. Campbell, Kentucky, on December 18, 1953, with a 24-hour history of severe generalized headache, chills, fever, and stiff neck.

Sixteen days before admission, on November 22, 1953, the patient had been examined in the emergency room of this hospital because of severe pain in and above the left eye. This began several days before and the patient stated that he had had "sinus trouble" previously. There had been very little drainage from the nose. The examining physician noted exquisite tenderness in the left frontal region and injected procaine into the left supraorbital foramen. This afforded nearly complete relief from the pain. The next day the patient was examined by the otolaryngologist, who noted nasal congestion in the region of the left middle meatus; a small amount of purulent material escaped during irrigation of the left frontal sinus. There was no fever. The patient returned the following day and complained of continuing left frontal pain. There is no record of the administration of any antibiotic medication, and the patient was not examined again until the day of admission to the hospital.

The patient's wife stated that during the two weeks prior to admission, he experienced almost continuous left frontal pain and headache but she did not notice any nasal discharge. There was no fever or other systemic reaction until the day prior to admission, when the symptoms noted above developed. The patient's wife also stated that he had recurring attacks of "sinus trouble" in the past but no other relevant illness.

On admission he was observed to be an acutely ill man who dozed frequently. The rectal temperature was 102° F., pulse 88 per minute, respiration 24 per minute, and blood pressure 128 systolic, 78 diastolic. The ears appeared normal. The pharynx was only slightly infected. The lungs were clear to percussion and on auscultation. Examination of the heart and abdomen was not contributory. There was much resistance to passive flexion of the neck. The visual fields were not examined, but the neurologic examination was in all other respects normal.

The initial white blood cell count was 14,200 per cu. m.., of which 95 per cent were polymorphonuclear leukocytes, with a predominance of metamyelocytes. The hemoglobin was 14 gm. per 100 cc. Urine examinations were negative. Serologic tests for syphilis were negative.

A lumbar puncture was performed on the day of admission. The initial pressure was equivalent to 300 mm. of water. About 10 cc. of turbid fluid was removed, and the closing pressure was equivalent to 260 mm. of water. The fluid contained 1,900 white blood cells per cu. mm., of which 98 per cent were polymorphonuclear leukocytes. The sugar content was 69 mg., chlorides 747 mg., and protein 41 mg. per 100 cc. of cerebrospinal fluid. The patient received no intravenous glucose until after the lumbar puncture. A gram-stained smear of the cerebrospinal fluid was thought by one observer to demonstrate a few gram-nega-

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tive cocci, but others considered the smear to be negative. A culture for bacteria yielded no growth. A blood culture was sterile after 24 hours of incubation. Alpha and beta streptococci were the predominant organisms recovered from the throat culture. Radiographs of the chest and skull were interpreted as showing no diagnostic abnormalities. The pineal gland was not calcified.

The patient was treated with intravenous dextrose and saline containing 2,000,000 units of crystalline penicillin. In addition, 400,000 units of crystalline penicillin was given intravenously every four hours.

During the night of admission the patient's temperature rose to 102° F., but when examined the next morning the rectal temperature was 99° F. and he appeared improved. He drank water from a glass, asked the nurse for a bed pan, and answered questions, although the examining physician noted that he was not well oriented. Within the next two to three hours the patient became much worse. He thrashed about in bed, rolled back and forth, and complained of severe headache. When reexamined at 9:30 a.m., he was stuporous but the pupils were regular and equal. The only other abnormal finding was an equivocal plantar response on the right side. He had a shaking chill, and the temperature rose to 103° F. At 11:00 a.m. the pulse was 80 per minute and the blood pressure 180 systolic and 80 diastolic. Respirations were labored and irregular; the left pupil was widely dilated and did not constrict in response to a bright light. The right pupil was small and did not react to light. The optic fundi appeared normal. The left arm and leg were extended, rigid, and did not move in response to pain. The right arm and leg resisted passive movement in every direction. The deep tendon reflexes were generally brisk; the left plantar response was extensor, the right flexor.

At 1:00 p.m. the day after admission, an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. SPROFKIN: In summary, a 29 year old man, with a past history of sinus disease, experienced an acute attack of left frontal sinusitis during the three weeks prior to hospitalization. On the day preceding admission headache became much more severe, and a profound systemic reaction ensued with chills, fever, stiff neck, and lethargy.

There is no doubt that he had an acute purulent frontal sinusitis. We can also be certain that the development of fever, chills, stiff neck, and apathy in such a patient indicates intracranial extension of the infection. The differential diagnosis includes epidural abscess, thrombosis of the superior longitudinal sinus, subdural empyema, bacterial leptomeningitis, and brain abscess.

Intracranial suppuration confined solely to the epidural space would not be likely to result in such a severe illness with meningeal and focal neurologic signs. If epidural pus was present here, it would be only of passing interest as a sign of an underlying subdural empyema or of an intracerebral abscess.

The cerebrospinal fluid findings of increased pressure, pleocytosis with predominantly a polymorphonuclear response, and a normal sugar content with negative smears and cultures for bacteria are characteristic of an aseptic meningeal reaction. The protein content seems remarkably low under the circumstances. This type of meningeal reaction is often associated with brain abscess or a subdural collection of pus and is not a bacterial leptomeningitis.

Kubik and Adams[1] have pointed out that the cell count is usually lower and that lymphocytes predominate in the cerebrospinal fluid of patients with cerebral abscess. However, in a recent review of the subject of subdural purulent collections, Stern and Boldrey[2] concluded that the number and type of leukocytes in the cerebrospinal fluid were not of much value as aids in differential diagnosis.

In most cases of brain abscess, the onset is more insidious, the course more protracted, and the temperature normal or only mildly elevated. Stiff neck is not commonly encountered with brain abscess unless the infection has extended into the meninges. Although these considerations do not categorically exclude the possibility of an acute fulminating brain abscess in this case, they are usually relevant in differentiating between a subdural accumulation of pus and an intracerebral abscess.

Having excluded bacterial leptomeningitis, extradural abscess, and brain abscess, the remaining diagnostic possibilities are thrombosis of the superior sagittal sinus and subdural empyema. As Kubik and Adams have noted, there is great clinical similarity between subdural empyema and thrombosis of the superior sagittal sinus. In four of their 14 cases of subdural empyema, there was a coexisting sinus thrombophlebitis. On the other hand, in a series of 16 cases of subdural purulent collections reported in 1952 by Stern and Boldrey,[2] there was not one instance of major sinus thrombosis.

If a sinus thrombosis is present in this patient, it will probably be in association with a subdural empyema. Occasionally, a focal osteomyelitis of the frontal bone will also be found in cases of subdural empyema following frontal sinusitis. The superficial cortical veins may be thrombosed, with hemorrhagic necrosis of the regions which they drain. The leptomeninges subjacent to the subdural empyema are usually the site of an aseptic inflammatory reaction. Although otitis media was probably the most common antecedent infection in the prepenicillin era, since 1943 frontal sinusitis has been commonly reported as the underlying infectious disorder in subdural purulent collections.[3]

In conclusion, the clinical pattern of exacerbation of a chronic frontal sinusitis with localized pain and tenderness and headache of increasing severity, becoming generalized, associated with high fever and stiff neck, followed by rapid deterioration with stupor and focal neurologic signs, is sufficient evidence for a diagnosis of subdural empyema. I would suspect that this was also the preoperative diagnosis of the physicians who cared for this patient on the wards.

CLINICAL DIAGNOSIS

Subdural empyema, left.

DISCUSSION

DR. DODGE: As Dr. Sprofkin predicted, a subdural empyema over the left cerebral hemisphere was found at operation. For the reasons he cited, our preoperative diagnosis was focal intracranial suppuration adjacent to the leptomeninges. Subdural empyema was the favored diagnosis but we did not exclude the possibility of a left temporal lobe abscess, because at the time of surgery details as to the evolution of the illness, including the history of acute sinusitus three weeks before admission, were not available to us.

In addition to the diseases Dr. Sprofkin mentioned, acute necrotizing hemorrhagic encephalopathy was considered by us in the differential diagnosis. Adams, Cammermeyer, and Denny-Brown[4] have emphasized that the clinical and cerebrospinal fluid findings in this condition closely resemble those found in subdural empyema, and our experience is in accord with this. Also, we quite recently encountered a patient with acute "inclusion encephalitis" probably due to the virus of herpes simplex, in whom the clinical and laboratory data were very similar to those found here. A history or the discovery of an acute frontal sinusitis, mastoiditis, or lung abscess usually provides the essential clue to the correct diagnosis.

In the present case, the rapid development of a fixed, dilated left pupil, coma, and rigid extension of the left arm and leg suggested that the left temporal lobe uncus had herniated through the incisura of the tentorium and that immediate surgical treatment was mandatory. The patient was operated upon under local anesthesia by Dr. Charles W. Cure, who performed a left posterior parietal trephination. The dura was opaque, and when it was punctured a large quantity of foul-smelling, yellow-green pus escaped. Another trephine hole was made in the left frontotemporal region and the subdural space was thoroughly irrigated with saline. Drains were left in the subdural space for several days. It was estimated that there had been in excess of 100 cc. of subdural pus present. Two days later the left frontal sinus was explored and

several areas of subsiding infection were seen on the posterior mucosal wall. There was no evidence of osteomyelitis of the frontal bone, however, and the intracranial spread of infection was probably by way of diploic veins.

The patient was treated with large doses of intramuscular penicillin and streptomycin. Chloramphenicol was added later. Antibiotics were continued for approximately a month. Two organisms, *Micrococcus tetragenes* and an unidentified gram-negative rod, were grown from the purulent material recovered at operation. The former was sensitive in vitro to therapeutic doses of Chloramphenicol, while the latter organism could not be subcultured and its sensitivity tested. The patient remained febrile for two and a half weeks but had no fever or sign of infection during the subsequent six months of hospitalization. The cerebrospinal fluid was reexamined several weeks after admission and was found to be normal.

The course of neurologic findings in the postoperative period was quite typical of subdural empyema and proved to be of considerable interest. The response to the removal of pus was dramatic. The patient roused and began moving the left side while still on the operating table. He remained somnolent for two weeks after operation but could be aroused. A right hemiplegia, homonymous hemianopsia, and aphasia were noted within two days after surgery, and the patient began having repeated, right-sided seizures. These signs were attributed to secondary thrombophlebitis of cortical veins and consequent cerebral infarction. This is a common complication or accompaniment of subdural empyema, as Dr. Sprofkin stated.

The hemiparesis cleared completely within a month, but the aphasia resolved slowly. Six months later the patient was still confused by complicated written or oral commands, and he frequently mispronounced words. The homonymous hemianopsia persisted unchanged, and despite anticonvulsant medication the patient continued to have an occasional seizure.

It might be argued that the surgical procedures done in this case were not sufficiently extensive, since an osteoplastic craniotomy was not performed and the mesial surface of the hemisphere was not inspected, as List[5] and Keith[6] advise. These authors and others have emphasized the frequency with which the interhemispheral fissure contains purulent material. Most neurosurgeons advise an extensive craniotomy, pointing to the frequent failure of less extensive surgery to cure. Nevertheless, the patient presented here has shown no evidence of continuing infection or progressive intracranial disease, and I think we can safely assume that treatment was adequate.

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Diagnosis and Treatment of Acute Subdural Empyema

Carl Felix List, M.D.

THE TERM SUBDURAL EMPYEMA designates an accumulation of pus underneath the dura but outside of the subarachnoid space. Until recently, the clinical diagnosis of this condition has been frequently missed and confused with that of meningitis or intracerebral abscess. Actually, subdural empyema is a characteristic clinical entity in its own right; it is certainly one of the most vicious forms of intracranial infection and likely to end fatally unless immediate drastic treatment is given. With the advent of sulfonamides and antibiotics the incidence of intracranial infections has been reduced materially and their course has been better controlled. The undiagnosed and inadequately treated cases, nevertheless, still offer a major challenge.

PATHOGENESIS

For a better understanding of the problem involved, the pathogenesis of subdural empyema must be discussed first. An acute pyogenic infection may reach the subdural space in five different ways:

1. The infection may be introduced directly, for example, by a contaminated penetrating wound of the skull.

2. The infection may start from an adjacent extracranial focus and stepwise extend by continuity into the subdural space; for example, an acute frontal sinusitis may produce osteomyelitis of the adjacent frontal bone, then an epidural abscess, and finally, after penetrating the dural barrier, a subdural empyema.

3. Septic thrombophlebitis is a third mode of infection; in purulent pansinusitis, for example, there develops thrombophlebitis of mucosal veins, later of orbital veins. This septic thrombosis extends through the diploic channels into the dural veins and sinuses and finally into the cerebral veins. The exposed course of some of the bridging dural and cortical veins favors the formation of subdural empyema. At the same time, the course of infection is frequently marked all along its path by orbital cellulitis, subperiosteal abscess, osteomyelitis of the skull, epidural abscess, and intracerebral abscess. This probably is the most common pathogenesis of subdural empyema.

4. Subdural empyema may be a sequela of purulent leptomeningitis.

5. On rare occasions, subdural empyema

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develops on the basis of a hematogenous infection from a distant focus; for example, in infants a chronic subdural hematoma may become secondarily infected in the presence of existing bacteremia.

Once the infection has reached the subdural space, it spreads rapidly over the cerebral convexity without meeting obstacles. It often enters the interhemispheral fissure and extends from there around the falx to the other side (especially when the suppuration originates at the orbital surface of the frontal poles).[1,2] With the bedridden patient in recumbent position, the subdural exudate gravitates to the posterior part of the cerebral hemisphere, particularly to the space between the falx and tentorium. Thus, acute subdural empyema develops progressively in an anteroposterior direction, affecting either the dorsolateral surface of the hemispheral convexity or the interhemispheral fissure or both regions. Since the most common source of subdural empyema is an infection of the paranasal sinuses, the causative organisms usually are anaerobic streptococci and/or staphylococci. Otogenic subdural empyema is very rare. In cases of hematogenous origin, the organisms may come from the gastrointestinal tract (*E. coli, Salmonella*).

CLINICAL SYMPTOMATOLOGY AND DIAGNOSIS

The clinical course of subdural empyema is rapid and grave. As a rule, patients are adolescents or young adults, with the male sex prevailing. The typical story begins with acute pansinusitis which had been treated inadequately or not at all. Early inflammatory edema of the eyelids may be the first manifestation of extension of the infection. After a relatively quiescent period of one to two weeks, during which the infection seems to subside, an abrupt change occurs in the patient's condition. Severe unilateral headaches develop and are accompanied by clouding of sensorium, symptoms of meningeal irritation, a sudden elevation of temperature, and a leukocytosis of 30,000 or even more. The disease now progresses rapidly to a dramatic climax. Within hours jacksonian convulsions occur and are soon followed by progressive hemiparesis and coma. If the subdural empyema occupies the frontoparietal convexity and the region over the sylvian fissure, the convulsive movements involve eyes, face, and the upper extremity. A faciobrachial hemiparesis ensues with aphasia (in a left-sided lesion). With increasing hemiparesis there is usually paralysis of conjugate horizontal gaze to the paretic side. Interhemispheral empyema, on the other hand, exhibits quite a different clinical syndrome.[2] Here the convulsions begin in the lower extremity, and later may involve both the opposite leg and arm but spare the face. Thereafter, sensory and motor paresis develops in the lower extremity first; eventually the hemiplegia becomes complete with the exception of the face. Homonymous hemianopsia is another even more significant diagnostic sign. Visual field defects and sensory changes may be detected only in the early stage, but when the patient's consciousness becomes progressively clouded, their presence is difficult to demonstrate.

The eyegrounds frequently remain normal in acute subdural suppuration, or reveal only venous stasis or early papilledema. Roentgenograms of the skull disclose evidence of pansinusitis and sometimes also of osteomyelitis, but give no specific diagnostic help. If the patient is seen at an early stage of the intracranial suppuration, an erroneous diagnosis of purulent leptomeningitis is understandable; in fact, lumbar puncture may demonstrate a slightly cloudy fluid under high pressure. The cell count in the cerebrospinal fluid may vary between several hundred to two thousand polymorphonuclear leukocytes, but no organisms are present, nor is the sugar level appreciably decreased. The protein value is often relatively high. These findings point to an adjacent focus with severe leptomeningeal reaction, but tend to rule out direct bacterial invasion of the subarachnoid space.

The best method to confirm the clinical diagnosis of subdural empyema is trephination over the suspected area. This method permits verification of the lesion, identification of the causative organism, and, at the same time, surgical drainage of pus. In acute subdural empyema neither arteriography nor ventriculography is advisable. The trephine opening must be made close to the midline if an interhemispheral empyema is suspected; here pus may not be obtained until the exploring cannula touches the falx.

TREATMENT

Acute subdural empyema must be regarded as an absolute emergency. Unless vigorous treatment is given promptly, the outcome will be fatal. Two objectives must be attained: control of infection and removal of the pus. One cannot afford to waste time by awaiting proper identification of the organisms before selecting the appropriate drug. Sulfonamides and antibiotics are immediately administered parenterally in large doses before surgery is attempted. The author has used 100,000 to 300,000 units of aqueous penicillin every 3 hours intramuscularly, combined in some cases with 0.3 gm. streptomycin, and sulfadiazine in doses of 6 to 8 gm. in 24 hours (intravenously). Fortunately, sensitivity studies have shown that the organisms usually respond well to this empirically chosen drug combination. On the other hand, with ever increasing bacterial resistance to penicillin and streptomycin, newer antibiotics such as Terramycin, Erythromycin, Achromycin, and Bacitracin serve as effective substitutes. Even though sulfonamides and antibiotics inhibit the spread of the infection and permit mobilization of the defenses of the body, it would be a serious mistake to rely entirely on drugs and to procrastinate surgical measures. The extremely grave condition of most patients makes an immediate operation imperative. In the early stage the pus is liquid and easily drained, but prolonged treatment with antibiotics transforms it into a chronic subdural granuloma with inspissation of pus which is difficult to remove.

The primary trephine opening should be placed over the presumptive site of the lesion. If a dorsolateral convexity empyema is suspected, the first burr hole is made in the posterior lateral frontal region; in case of an interhemispheral suppuration, the burr opening is made in the posterior parietal region, close to the midline. If pus is encountered, the drill hole is enlarged to a diameter of at least 3 cm. and the exposed dura excised. Two or three additional trephine openings of similar size are then made in order to make the entire empyema accessible to drainage. In interhemispheral empyema, the bony openings should be placed in a parasagittal plane from the frontal region to the occiput and an additional opening should be made low in the temporo-occipital region to drain the epitentorial space (figure 1).

Primary evacuation of the empyema is essential since remaining loculations of pus may lead to the formation of a chronic subdural granuloma. The exudate is more easily evacuated after collapsing the cerebral hemispheres by spinal puncture. This maneuver, suggested by Kahn,[3] greatly facilitates the removal of an empyema of the convexity but is less effective in interhemispheral empyema because the bridging veins prevent wide separation of the brain from the falx and the tentorium. After the pus has been thoroughly evacuated by aspiration and subsequent irrigation with saline solution, a soft rubber catheter (French No. 8 or 10) is introduced through each of the burr holes into the subdural space (either of the convexity or of the interhemispheral or epitentorial regions) and left in place (figures 2 and 3). The scalp incisions are then closed without additional drainage, unless there is osteomyelitis of the skull. Starting from the time of surgery, solutions of penicillin and streptomycin or Bacitracin are injected into each of the inlying catheters three times daily for three to six days. Even though systemically ad-

ministered penicillin or streptomycin readily enters the subdural space, a much higher and sustained concentration of antibiotics is attained by such additional topical instillation. The author has been using an aqueous solution containing 5,000 units of penicillin (and on occasion, 25 mg. of streptomycin) per ml. A total of 10 to 16 ml. of this solution is injected into the catheters which are kept closed. In the first 24 to 48 hours some purulent drainage emanates from the catheters, but later this stops and the return flow of antibiotic solution from the catheters remains clear. There is a certain risk that large doses of concentrated penicillin solution in contact with the cerebral cortex may evoke convulsions, especially in patients who are more prone to seizures because of the acute irritative cortical process. Under such circumstances the occurrence of convulsions must be accepted as a calculated risk, which can be reduced by anticonvulsant therapy. In the first two or three days of treatment patients show some improvement in their state of consciousness and the temperature may approach normal, but usually there is little change in the neurologic signs and the focal convulsive seizures continue unabatedly. After four to six days, when the previously progressive course of the disease seems to be definitely arrested, the inlying catheters are removed but the systemic use of antibiotics is continued. By this time the convulsions have ceased as a rule, and the patient is able to take medications (sulfonamides) orally. After the fifth day, the neurologic signs tend to improve rapidly, yet it is not unusual to observe phenomena of rising intracranial pressure. The scalp bulges over the trephine openings, a bilateral sixth nerve paresis may develop, and the papilledema increases with occurrence of multiple retinal hemorrhages. These new signs of increased intracranial pressure do not ordinarily indicate further complications; they usually subside slowly and spontaneously after several weeks. It has been the author's practice to continue the systemic use of penicillin and sulfonamides for at least two or three weeks postoperatively, or longer in the presence of osteomyelitis. The sulfa level in the blood should be maintained at no less than 6 mg. per cent during the critical first ten days.

Several neurosurgeons[3,4,5] follow a similar procedure as described here, but others advocate more drastic surgical measures. Glass[6] and LeBeau,[7] for example, propose to turn a large osteoplastic flap over the empyema, a procedure which, in the author's opinion, unnecessarily aggravates the risk in critically ill patients. Keith and McKenzie[1] remove a long median or paramedian strip of bone for better drainage of interhemispheral suppuration; although this management was successful in their three cases, it has the disadvantage of prolonging the operation and of depriving the superior longitudinal sinus of its bony protection.

It is essential to verify the patient's recovery anatomically by pneumographic studies; as a rule, it is best to perform a ventriculogram from the uninvolved side before the patient's discharge. If the investigation is done later on, pneumoencephalography may be preferable. Without these control air studies, residual abscesses may be overlooked. This happened in the author's first case of interhemispheral empyema where chronic residual subdural granulomas required two additional operations. If the subdural empyema is healed, pneumography reveals moderate general dilatation of the ventricular system. On the involved side there may be greater enlargement and traction deformity of the ventricles and obliteration of the subarachnoid spaces of the convexity.

The clinical end results are gratifying but by no means perfect. All of the author's last seven consecutive cases, treated as described above, recovered. Six patients are alive now and one died several years postoperatively from an unrelated illness. In general, the three cases of interhemispheral empyema have fared better than the four

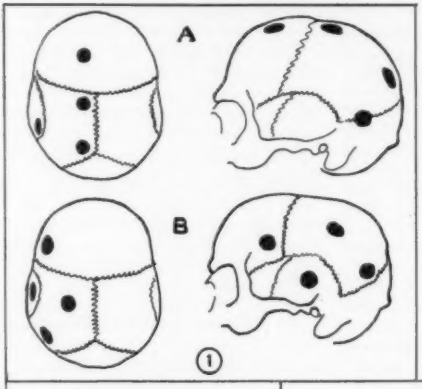
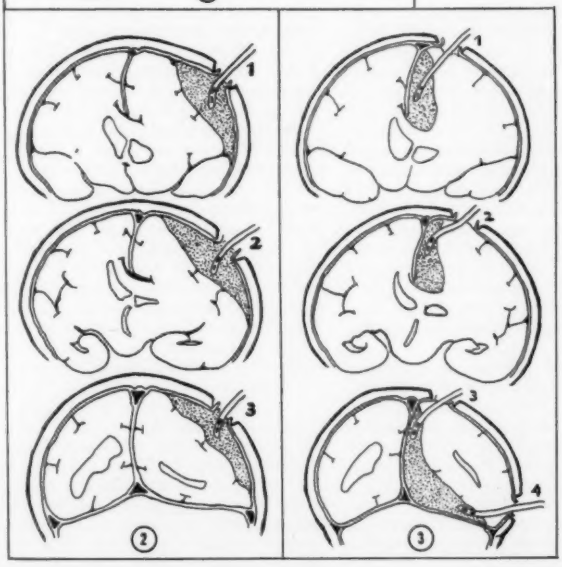


FIG. 1. Suggested position of trephine openings. *A*. In interhemispheral subdural empyema. *B*. In subdural empyema of the hemispheral convexity.

FIG. 2. Diagrams to show the insertion of catheters into a subdural empyema of the hemispheral convexity.

FIG. 3. Diagrams to show the insertion of catheters into an interhemispheral subdural empyema.



patients with convexity empyema. Two of the interhemispheral group have no neurologic residuals whatever, but the third has a permanent homonymous hemianopsia caused by the resection of the occipital lobe (for chronic granuloma). No case of this group has had convulsive seizures after the early period of convalescence. Among the convexity group all have recovered from their hemiparesis, but two patients with lesions over the dominant left hemisphere still suffer from persistent aphasia. All four of these patients have had occasional convulsive seizures. The high incidence of such aftereffects is explained by cicatrisation of important cortical areas, following the widespread thrombophlebitic and meningeal inflammatory process.

ILLUSTRATIVE CASES

Case 1.–Subdural empyema of the left hemispheral convexity.

A 14 year old boy was admitted to the hospital on March 18, 1954. Four weeks prior to admission, the patient had sinusitis. Following a tonsillectomy a week later he developed fever, increasing left frontal headache, and purulent nasal discharge. One week prior to admission, a brief attack of inability to talk and numbness of the right arm occurred but there were no convulsive movements. He was then given penicillin and streptomycin for a few days, and he improved except for the persistence of his headaches. The day before admission, the headache became very severe, the left eyelids were swollen, the temperature rose, and total aphasia and paresis of the right arm ensued.

Examination showed a gravely ill, lethargic, dehydrated boy with a temperature of 102.2° F., pulse 20, respirations 14, and blood pressure 126/70. There was subacute left pansinusitis with profuse purulent postnasal drainage.

He responded slowly, exhibiting predominantly expressive aphasia. The left eyelids and the adjacent frontal scalp were edematous and the entire left half of the skull was tender to percussion. Considerable nuchal rigidity and a positive Kernig sign were present. Early papilledema (⅓ diopter on the right and 1 diopter on the left), right-sided homonymous hemianopsia, and paresis of conjugate gaze to the right were noted. There was severe right hemiparesis with complete paralysis of the arm. Sensation appeared to be diminished on the entire right side.

The urine contained albumin and granular casts, and the leukocyte count was 29,800. Blood culture remained sterile. The roentgenograms of the skull showed left pansinusitis with early osteomyelitis of the frontal bone adjacent to the superior wall of the left frontal sinus.

A diagnosis was made of left subacute purulent pansinusitis, early osteomyelitis of left frontal bone, and subdural empyema over the left hemispheral convexity.

At operation on March 18, 1954 a very large acute subdural empyema was found covering the entire convexity of the left hemisphere, with the exception of the posterior parasagittal frontal region where osteomyelitis of the skull and a large extradural abscess were encountered. The subdural pus was drained through three enlarged trephine openings (anterior sylvian, posterior parietal, and temporo-occipital) and the extradural abscess through an additional parasagittal frontal craniectomy of oblong shape. The brain showed cortical thrombophlebitis and hemorrhagic infarctions. Rubber catheters were placed through each of the bony openings; three of the catheters were introduced into the subdural space, the fourth through the frontal opening into the epidural space. Aqueous penicillin, 160,000 units, was injected into the catheters (40,000 units each). In the postoperative period the patient received systemically 2.4 million units of aqueous penicillin and 6 gm. of sulfadiazine daily. In addition, the catheters were injected three times daily with 10 ml. of solution containing 50,000 units of penicillin. Culture of the pus yielded a combination of *streptococcus viridans, hemolyticus,* and nonhemolytic staphylococci; all these organisms were strongly sensitive to penicillin.

Little change occurred during the first two postoperative days, but on the third day the temperature dropped to 99.4° F. and a jacksonian attack occurred in the right leg. On the fourth day the patient responded better and his temperature had become normal. The following day he took fluids by mouth. The catheters were removed and replaced by Penrose drains. On the sixth day a lessening of the meningeal irritation was noted, yet a bilateral sixth nerve paresis had become evident. One week postoperatively his general condition continued to improve and he was able to move the right leg. On the twelfth day he was sitting up, and after two weeks he was walking; the papilledema began to subside but the bilateral sixth nerve palsy was still present. Sulfadiazine was discontinued after three weeks. Check-up ventriculogram on the twenty-seventh postoperative day showed moderately dilated ventricles, moreso on the left. At the time of his discharge on the thirty-third day, the wounds had healed well. He was alert, but showed expressive aphasia with fair understanding of speech. There remained a mild paresis in right arm and face but he walked normally. The eyegrounds were normal but right homonymous hemianopsia and right-sided abducens weakness persisted. Two and a half months postoperatively, the hemianopsia had partially receded and showed improvement in lower quadrants, and the sixth nerve paresis had disappeared. The other neurologic signs were unchanged. When last seen 11 months postoperatively, the aphasia had much improved, but a few convulsions had occurred.

Comment: The ill-advised tonsillectomy in the presence of active pansinusitis may have precipitated the intracranial suppuration. Unfortunately, permanent irreversible damage was caused by septic thrombophlebitis of cerebral veins.

Case 2.—Left interhemispheral subdural empyema.

A 16 year old girl was admitted to the hospital on June 28, 1952. Two weeks prior to admission, the patient developed an acute sinusitis after swimming, with profuse nasal discharge, fever, and frontal headaches. She was treated with chloromycetin because she was supposedly sensitive to penicillin. Three days prior to admission, she had a chill which was followed by fever up to 104° F. She also complained of severe left frontotemporal headache and of stiff neck. The next day, she became confused and complained of numbness in her right leg; the following day (one day prior to admission) the right leg had become paralyzed. There were no convulsive seizures.

Examination revealed an acutely ill, adolescent girl, semistuporous, yet responding verbally without gross aphasia. Her temperature was 101.2° F. rectally, pulse 84, and respirations 24. There was evidence of subsiding pansinusitis. Her neck was rigid; photophobia and positive Kernig sign were noted. The left frontal region was tender to percussion. Early papilledema without elevation was present. The visual fields were normal and there was no facial weakness, but the right upper extremity was a trifle paretic. Flaccid paralysis of the right lower extremity and considerable paresis of the right abdominal muscles were evident. The right abdominal reflexes were absent; all deep reflexes were present on the right and a positive right Babinski sign was elicited. Disturbance of position and tactile sensations and of graphesthesia could be demonstrated in the right lower extremity.

Roentgenograms of the skull revealed clouding of the left maxillary antrum. There was a leukocyte count of 17,250. On lumbar puncture the cerebrospinal fluid had a pressure of 340 mm. of water and contained 22 lymphocytes, 82 mg. per cent protein, and 120 mg. per cent sugar but no organisms.

The clinical diagnosis was made of acute left interhemispheral empyema following pansinusitis.

At operation on July 1, 1952 three parasagittal trephine openings were made on the left side. In the prefrontal region there was suggestive evidence of osteomyelitis of the skull and a large epidural abscess. Thick pus was evacuated from the interhemispheral fissure both through the anterior parietal and posterior parietal trephine openings. A rubber catheter was introduced through each of the burr holes into the subdural interhemispheral space and a fourth catheter placed into the epidural abscess cavity; 20,000 units of penicillin (in 4 ml.) were instilled three times daily into each of the catheters. In addition, the patient received 1.6 million units of penicillin and 8 gm. of sulfadiazine daily. From the pus, hemolytic streptococci were cultured which fortunately proved highly sensitive to all antibiotics except Bacitracin.

By the second postoperative day the patient was more responsive, her temperature had come down, and the meningeal irritation lessened, but the neurologic signs remained unchanged. From the third to the eighth postoperative days she showed occasional right jacksonian seizures involving face and arm. Temporary aphasia and moderate paresis of the right arm had developed. The catheters were removed on the sixth postoperative day. The paralysis of the right lower extremity began to clear up at the same time and subsequently showed further rapid improvement. On the other hand, the patient developed progressive bilateral sixth nerve palsy and papilledema up to 3 diopters elevation, which persisted at the time of her discharge on the twenty-ninth postoperative day; otherwise, all neurologic signs and symptoms had then completely cleared up. A check-up ventriculogram shortly before discharge was perfectly normal. Subsequently the patient was seen repeatedly in the office. Her ocular disturbances gradually subsided after two months and she has been completely well ever since. The convulsions did not recur and her electroencephalogram was normal.

Comment: The virulence of the original infection may have been somewhat mitigated by the treatment with Chloromycetin. The occurrence of seizures only during the early postoperative period suggests possible spread of the cortical thrombophlebitis or a local reaction to topical penicillin instillation. The late manifestations of increased intracranial pressure and their slow subsidence seem to be quite characteristic. The end result was remarkably good in this case.

SUMMARY

Acute subdural empyema is a particularly vicious intracranial infection which ends fatally unless promptly diagnosed and treated.

Acute subdural empyema develops most frequently from pansinusitis by septic thrombophlebitic propagation.

The clinical syndrome is characteristic and depends on whether the suppuration is located over the hemispheral convexity or in the interhemispheral fissure.

Modern treatment consists of evacuation of pus through multiple trephine openings, intermittent irrigation of the subdural space with antibiotic solutions, and prolonged systemic administration of large doses of antibiotics and sulfonamides.

Although mortality is low, permanent neurologic sequelae may not be preventable.

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■ We have now to say a few words on a theory which was first proposed by Bellingeri, and had the good fortune of being accepted by an eminent physiologist, Prof. Valentin, of Bern. According to these experiments, the motor nerve-fibres which go to the extensor muscles pass in the posterior columns, while those which go to the flexor muscles pass in the anterior columns. We have already said that a section of the posterior columns does not produce any kind of paralysis, so that they are not more for extension than for flexion. But the question remains whether the other posterior parts of the spinal cord are, or are not employed for one of these kinds of movements more than for the other. To solve this question, we divide in the dorsal region, the posterior half of the spinal cord in a mammal, and nearly the whole of the anterior half of this organ in another, and we find that all the muscles seem to be almost completely paralyzed in the abdominal limbs, the flexors as much as the extensors, in the two animals. If some pathological facts observed in man, and of which we will speak in another lecture, appear to be different from these facts, we will show there was in them an irritation, and not a destruction or a section, of certain parts of the spinal cord or of its nerves.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

CASE REPORT

Effect of Anosmia on the Appreciation of Flavor

Edward C. Clark, M.D. and Henry W. Dodge, Jr., M.D.

A CENTURY AGO a controversy existed as to the role of the lingual nerve in the determination of taste and flavor. In the past 100 years, however, considerable evidence has been collected supporting the assumption of Brillat-Savarin[1] and others that the flavor of substances is largely, if not altogether, dependent on olfaction.[2,3] Moncrieff[4] has stated the opinion that "people suffering from loss of smell lose also what they call their 'sense of taste,' but which is really their odour component of the flavour." Best and Taylor[5] have said that blocking of the nasal passages by an upper respiratory infection seems to blunt the appreciation of taste, and it may then be impossible to distinguish between the taste of an apple and a pear, or a potato and a turnip. While observing that other factors may be of importance, such authors of physiology and psychology textbooks as Starling,[6] Geldard,[7] and Andrews[8] have noted that the flavor of substances depends for the most part on olfaction. Little opposition to this assumption is noted in the pertinent literature. However, Hutchison,[9] Crosland, Goodman and Hockett,[10] and Leigh[11] have reported cases of patients said to be suffering from anosmia who apparently continued to enjoy and recognize the flavor of various foods.

In view of the difference of opinion revealed in the literature as to the importance of olfaction in the appreciation of flavor, the following report of a case may be of interest.

REPORT OF A CASE

A 44 year old white married woman, examined at the Mayo Clinic in May 1953, complained of progressive loss of her sense of smell (complete for more than one year) and of recent onset of headaches. The results of various examinations led to the determination that she was suffering from a tumor located in the region of the tuberculum sellae turcicae in the grooves for the olfactory nerves. Subsequently bilateral frontal craniotomy was performed and a meningioma was removed from the olfactory grooves. Because of cerebrospinal rhinorrhea, the patient underwent reoperation in February 1954 for repair of the leakage which permitted the escape of fluid. At that time the surgeon demonstrated that the olfactory nerves had been completely destroyed.

After the repair operation, the patient was carefully questioned concerning her ability to enjoy flavors. She stated that as her sense of smell disappeared she had lost the ability to distinguish certain flavors. She recalled that

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approximately two years previous to her admission to the clinic she had become unable to taste chocolate. Similarly she remembered that she was unable to distinguish among spices and that pumpkin pie tasted like plain egg custard. Despite these exceptions, the patient stated that after she had lost her sense of smell she had continued to enjoy food and, while there may have been some blunting of taste, she did not think that she had lost her ability to distinguish most flavors.

Some time after her first operation the patient discovered that she could again taste chocolate. Insofar as she could remember, beefsteak tasted as it always had, and she felt certain that she could distinguish between pork and beef. She recalled, however, that she had mistaken lamb for veal. It was her impression that she could distinguish the various flavors of ice cream and sherbet. She regularly drank orange juice, pineapple juice, and tomato juice and ate grapefruit and stated that she was able to taste the flavor of all of these foods satisfactorily.

Except for olfaction, examination of the patient did not reveal evidence of neurologic or mental deficiencies. Examination of the patient's olfactory sense revealed that she could not identify any of the test substances including oil of wintergreen, camphor, cloves, ginger, or cinnamon. With the use of sugar, sodium chloride, quinine, and tartaric acid, it was found that the patient was able to identify sweet, salty, bitter, and sour sensations on both sides of the tongue. Sensory examination of the patient's mouth revealed that she could recognize heat and cold and pain and light touch on the tongue and mucous membranes. Two-point discrimination was normal on the tongue and lips. Vibratory sensation was present on the chin and teeth. She could distinguish the wetness or dryness, the size, shape, texture, and consistency of objects placed in her mouth.

The patient's ability to distinguish flavors was determined by having her close her eyes after which food was placed in her mouth by pouring it out of a cup or spoon. All solid foods were given in the shape of a cube to decrease the possibility of recognition of the food by its physical shape. Pulped and strained foods, juices, and artificially flavored gelatin also were used for the same purpose. The patient was encouraged to expectorate the food after tasting it. Her mouth was rinsed with cool tap water after each test and several minutes, at least, were allowed to elapse before a new test food was given. On being given the food to taste, the patient was asked to respond as to the identity of the food at the time of spitting it out and, shortly thereafter, to give a later opinion as to the afterflavor. The patient was tested for several days in March and again in August 1954.

As is shown in table 1 it is evident that this woman was able to identify a considerable number of foods, the flavors of which she said she could appreciate. Her long experience with cooking as a housewife was evidenced by her voluntarily and correctly identifying an apple as being of the "Delicious" variety. Later, when given a "Winesap" apple, she stated that it was not a "Delicious" or a "Wealthy" apple. She added that she might think it was a Winesap except for the fact that she did not believe Winesaps were in season.

While some of the foods that this patient failed to identify might well have been missed by a person with normal olfaction, it would appear that her ability to identify and appreciate flavor had been reduced by the loss of her sense of smell. Rather frequently the patient would fail to identify certain foods such as flavored gelatin. Nevertheless, when she did identify the gelatin correctly she said that she could appreciate the flavor and she did not feel that she was guessing. However, although she consistently identified ground nutmeg "by the feel of it," she said she could not appreciate its flavor.

COMMENT

Börnstein[12] and Crocker[13] have maintained that flavor is a synthesis of sensations derived from the olfactory nerves, taste buds, and other sensory end organs of the mouth. Thus, the taste buds on the tongue, the mucous membranes of the mouth, and the nasopharynx aid in distinguishing salty, sweet, sour, and bitter sensations. Pain enters into determining biting and burning sensations. Temperature is of importance in appreciating the hotness or coldness of food. Light touch, deep pressure, proprioceptive impulses from the muscles of mastication and tongue, vibratory sensation and other sensations by way of the teeth, two-point discrimination, the ability to appreciate wetness and dryness, and

TABLE 1
IDENTIFICATION OF FLAVORS

Date of test and substance used	*Initial response*	*Afterflavor*
March 3, 1954		
Raw "Delicious" apple	Apple	"Delicious" apple
Raw pear	Pear	Pear
Raw potato	Potato	Potato
Raw turnip	I don't know	I don't know
Whole clove	I don't know	It feels like cloves
Vanilla pudding	I don't know	I don't know
Chocolate pudding	Chocolate	Chocolate
Butterscotch pudding	I don't know	I don't know
Ground cinnamon	It burns like ginger	I can't taste it
Ground nutmeg	It feels like nutmeg	I can't taste anything
Clove powder	It burns like cloves	It tastes a little like cloves
Ginger powder	It burns like mustard	I can't taste it
March 9, 1954		
Orange gelatin	Orange jello	Orange jello
Cherry gelatin	I think it's cherry	Probably cherry
Lemon gelatin	I don't know	I don't know
Lime gelatin	I don't know; it's jello	I don't know
Strawberry gelatin	I don't know	I don't know
Cherry gelatin	I don't know	I don't know
Raspberry gelatin	I don't know	I don't know
Lemon gelatin	Lemon	Lemon jello
March 11, 1954		
Raw orange	Orange	Orange
Strained pear with added lemon juice	Pear	Pear
Strained spinach	Spinach	Spinach
Strained sweet potato	Squash	Squash or pumpkin
Orange juice	Vinegar	Vinegar
August 26, 1954		
Raw tomato	Raw tomato	Tomato
Raw pear	Raw pear	Pear
Baked apple	It's a soft fruit	Cooked apple
Boiled potato	Potato	Cooked potato
Raw carrot	I think it's that turnip	Turnip
Tomato juice	Tomato juice	Tomato juice
August 26, 1954		
Raw "Winesap" apple	Raw apple	Not a "Delicious" or "Wealthy"; "Winesap?"
Strained pear with added lemon juice	Apricots	Apricots
Cooked tomato	Cooked tomato	Cooked tomato
Raw turnip	Is it that turnip?	Turnip
Raw potato	Raw potato	Potato
Canned pear	Canned pear	Pear
Strained carrots	Is it squash? I don t like it	Might be squash
Raw orange	Orange	Orange
Applesauce	Apple	Applesauce
Pu'ped raw potato	Potato	Potato
Pear juice	It's very sweet	I don't know Apricot?
Carrot juice	It tastes a little like tomato	It is real sweet
Cold cooked mashed potato	It might be cooked potato	It tastes more like potato now
Apple juice	It is tart Orange juice?	Orange juice?
Banana	It's a banana	well as I did I don't taste it as
Orange juice	Tart fruit juice	I don't know
Cinnamon	I don't know	I don't know
Strained spinach	I don't like it	Strained peas
Clove powder	I don't know	It's a spice
Ginger powder	It's a spice	Spice
Nutmeg	It feels like nutmeg	I can't taste it
Chocolate drops	Chocolate	Chocolate
Raw onion	It's hot	Pepper
August 27, 1954		
Grapefruit juice	Might be grapefruit	I can't really tell
Orange juice	It's a fruit juice	Fruit juice
Raw apple	Apple	Apple
Raw pear	Pear	Pear
Raw potato	Potato	Potato
Raw turnip	Turnip	It doesn't have much taste
Tomato juice	Tomato juice	Tomato juice
Cooked onion	I think it's cooked onion	It feels like cooked onion; I can't taste it
Raw onion	Raw onion	Raw onion

stereognosis are all used by the individual in determining the size, shape, weight, texture, and consistency of foods.

In addition, the psychologic state of the person at the time of eating the food is of importance. This psychologic orientation is complex and includes, in part, the person's memory of the flavor of the food on previous occasions, the setting in which the food is now being eaten, the visual appearance of the food, and the sound made while chewing the food. Thus, olfaction, taste, and the somesthetic sensations derived from the structures in the buccal cavity, nasopharynx, and adjacent structures, as well as sight, hearing, memory, and the psycho-

logic state of the person at the time of tasting, all join in forming a composite of sensations which is identified by the subject as flavor at a cortical level of the brain.

With this concept of flavor in mind it would appear that the ability of this anosmic patient to enjoy the flavor of many foods, in contradistinction to the ability of other anosmic people whose cases are reported in the literature, may lie in her ability to utilize better the sensations derived from the sensory end organs in the buccal cavity, nasopharynx, and adjacent structures. Whether this ability to utilize better the sensations derived from the mouth and adjacent regions is attributable to some unrecognized difference in the sensory end organs of the buccal cavity and nasopharynx, to variations in central pathways of the brain, to varying psychologic factors, or to a combination of these factors is not yet determined and seems to warrant further investigation.

SUMMARY

The case of a 44 year old white woman with anosmia due to observed destruction of her olfactory nerves caused by a meningioma in the olfactory grooves is reported. Contrary to what might have been expected, the patient could identify and enjoy the flavor of many foods placed in her mouth. Although this patient may be an exception, our observation suggests that different persons vary in their dependence on olfaction in their appreciation of flavor.

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CORRECTION

On page 553 of the August issue of NEUROLOGY (Goldstein et al.: Experimental Allergic Encephalomyelitis Following Administration of Homologous Brain Lipid Fractions, 6:550-554, 1955), an error appears in table 2. The fifth and last group listed should read "Nondialyzable H_2O insoluble residue."

CASE REPORT

Acute Cerebral Venous Occlusion

Manifested by Spontaneous Subarachnoid Hemorrhage

Stefan Szancer, M.D.

THE FOLLOWING CASE is reported because of certain unusual features hitherto not mentioned in the literature dealing with the subject.

A 45 year old white man was admitted to the third neurology service of Bellevue Hospital with a history of sudden onset of severe headache radiating to the neck two days previously. The headache increased in severity, was not relieved by medication, and tended to concentrate in the left temporal region. A few hours before hospitalization the patient's wife noticed that his speech became unintelligible and she reported that several bouts of vomiting occurred.

The past history revealed some interesting data. Twenty years prior to admission the patient developed thrombophlebitis of both lower extremities, complicated at that time by pulmonary embolism and infarction. Five years prior to admission he had had an episode of mesenteric thrombosis with subsequent partial resection of ileum. He was treated intermittently with dicumarol. Six weeks before admission he was found resistant to a single test dose of dicumarol, but in the past this drug had been known to have lowered his prothrombin activity to 10 to 30 per cent of normal. There was no history of any dicumarol intake in the last weeks prior to admission.

On admission the patient was in acute discomfort, vomited frequently, and pointed repeatedly to his left temporal region. Blood pressure was 140/75 and pulse 60 per minute. Heart action was irregular, with frequent dropped beats. There were old healed surgical scars of the abdomen and evidence of thrombophlebitis of long standing in both lower extremities, but no evidence of any acute process. His legs were not swollen, hot, or tender.

Neurologic examination revealed aphasia, predominantly of the expressive type. There were no meningeal signs nor eyeball tenderness. Cranial nerves were essentially normal, but the left optic disk was hazy as compared with the right. Examination of the motor system showed weakness of the right upper and lower extremities. Deep tendon reflexes were hypoactive on the right. Coordination could not be tested. Sensation could not be accurately tested, but pinprick stimuli produced a response in form of symmetric facial grimacing and withdrawal of the extremities, moreso on the left.

Lumbar puncture on admission yielded grossly bloody spinal fluid under pressure of 300 mm. of water. The supernatant fluid was xanthochromic.

At that time a diagnosis of spontaneous subarachnoid hemorrhage, probably due to ruptured aneurysm of the circle of Willis, was made.

Clinical course was marked by rapid onset of coma, dilatation of the left and then of the right pupil, bilateral ankle clonus and Babinski signs. Bilateral papilledema became apparent, more marked on the left. The eyes were fixed in the mid-position and on passive turning of the head moved only to the left. There were no meningeal signs at any time.

The patient was given supportive therapy,

From the third division neurology service of Bellevue Hospital, and the department of neurology, New York University College of Medicine, New York City.

Read at a joint meeting of the New York Neurological Society and the section of neurology and psychiatry of the New York Academy of Medicine, May 11, 1954.

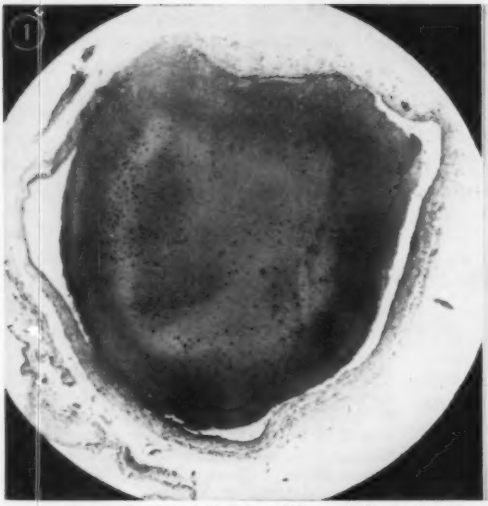

FIG. 1. Section of the left middle cerebral vein showing complete occlusion by the thrombus.
FIG. 2. Section of the left lateral sinus showing an incomplete occlusion by the thrombus.

oxygen, suction and hypertonic fluids, and antibiotics, but his condition deteriorated further, temperature rose to 105°, and he expired 60 hours after admission.

In addition to healed thrombophlebitis of both lower extremities, autopsy revealed thrombosis of the iliac veins and inferior vena cava, with organization, recanalization, and cavernous transformation. All these were considered old. There was a recent small thrombus in the inferior vena cava. Distal ileal resection was confirmed. Confluent lobular pneumonia was found. There were no abnormalities of the heart or of the arterial tree.

In the brain the vessels of the circle of Willis were found to be normal; there was no aneurysm. There was hemorrhagic destruction of most of the left temporal lobe and marked congestion of the cerebral veins in both hemispheres. Horizontal section showed a hemorrhage in the left lower parietal lobule, extending into the temporal lobe and destroying a large portion of the white matter. The hemorrhagic softening extended into the left external capsule. The left lateral ventricle was compressed and displaced to the right. There was also a hemorrhagic lesion of the right half of the midbrain. The left lateral sinus and the torcular were filled with firm blood clot. Section of the left middle cerebral vein showed complete occlusion with an organizing blood clot (figure 1). Section of the left lateral sinus demonstrated a partly organized blood clot attached to the wall of the sinus, but the lumen was still patent (figure 2). There was no evidence of inflammation in the sinus wall. The final diagnoses were: Intracerebral and intraventricular hemorrhage, secondary hemorrhage of the midbrain, subarachnoid hemorrhage, thrombosis of the left middle cerebral vein, and partial thrombosis of the left lateral sinus.

DISCUSSION

Cases of intracranial venous thrombosis are seen infrequently on neurologic wards. Venous thrombosis of noninfectious origin is rare, although described by Gowers in 1888;[1] all of his cases were associated with marasmus and cachexia or with failing circulation. In a recent series Barnett and Hyland[2] discussed 39 cases assembled over a period of years. In ten of these thrombosis occurred in patients with severe heart disease, mostly with right-sided cardiac failure. Seven patients were cachectic because of carcinomatosis, nutritional deficiency associated with mental deficiency, and so on. In five patients thrombosis occurred postoperatively and following head

trauma. In four cases venous occlusion was associated with arterial occlusion. Other cases occurred postpartum or were incidental to blood dyscrasias and fever therapy. In half of these there was evidence of recent thrombosis or embolism in other sites. Secondary subarachnoid bleeding misled the clinician in diagnosis on many occasions. Merwarth[3] described six cases of rolandic vein thrombosis associated with intracranial neoplasms, mostly with parasagittal meningiomas. Symonds[4] published five cases, of which two were of noninfectious origin occurring in women in the puerperium; the others following abortion. Hunter and co-workers[5] and Lhermitte and co-workers[6] described venous thrombosis in cases of congestive heart failure. Several puerperal cases were observed, and most recently Stevens[7] has made an extensive review of the literature on the subject. Barber[8] reported a case of thrombophlebitis migrans in which cerebral vein thrombosis was diagnosed retrospectively on the basis of history.

On the other hand, Barker[9] selected 79 cases of thrombophlebitis migrans out of his series of 1,011 consecutive instances of thrombosis collected in a five-year period in the Mayo Clinic. None of these patients showed any signs pointing to cerebral vein involvement.

The present case is unique in that the patient had none of the above mentioned predisposing causes, but a definite tendency to develop thromboses as documented by the past history of involvement of the veins in the lower extremities and abdomen, as well as pulmonary infarction and mesenteric thrombosis. At the time of the cerebral vein thrombosis no active process in any other organ was apparent clinically, nor was any found at autopsy. It could be said that he had a "thrombophilic diathesis," but this term does not explain but simply describes the condition. Clinically the subarachnoid hemorrhage was misleading.

In discussing this case one might raise the question of the use of anticoagulants. This cannot be answered on the basis of one case, but should be considered carefully in the management of patients who have a tendency to develop thromboses.

SUMMARY

A 45 year old man was admitted with a history pointing to an acute vascular disorder involving predominantly the left cerebral hemisphere. There was grossly bloody spinal fluid. This patient had a past history, extending over a period of 20 years, of venous thromboses involving the lower extremities and episodes of mesenteric thrombosis and pulmonary infarction.

Autopsy revealed a subarachnoid hemorrhage with hemorrhagic destruction of the left temporal lobe due to thrombosis of the left middle cerebral vein.

Literature dealing with the subject of noninfectious intracranial venous thrombosis is reviewed briefly.

Section of the brain and microscopic examination by Dr. Lewis D. Stevenson, associate professor of neuropathology, New York University College of Medicine.
Photographs by courtesy of the department of neuropathology of Bellevue Hospital.

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Neurology

BOOK REVIEWS

A Textbook of Neurology.

H. Houston Merritt, M.D. 1955. Philadelphia: Lea and Febiger. 746 pages. $12.50.

To a reviewer whose impulse is to groan with dismay when yet another textbook comes to his desk, the present one was a refreshing exception. It is, in the first place, plainly the handiwork of a clinician who knows his business well. The author's express conviction that clinical neurology is properly an aspect of internal medicine permeates the whole book; throughout its pages the discipline of neurology is presented against the background of contemporary medicine. It is this more than anything else that sets the book apart from most texts on the subject. A clear and simple exposition has enabled the author to include a great deal of essential factual material without crowding or skimming. Little time is wasted on moot points. In those conditions for which definitive treatment exists, it is presented clearly and specifically and in enough detail to be of practical use to the practitioner. Therapeutic fads are ignored or placed in proper perspective.

The organization of the book is somewhat unusual in that the subject matter is arranged along etiologic lines rather than according to diseases of separate structures. This is less artificial and leads to less repetition than one might at first think. In fact, such a plan, combined as it is with a full table of contents and an adequate index, makes the volume exceptionally suitable as a ready reference work for students. For the beginning student, however, a textbook devoted almost entirely as this one is to the consideration of diseases of the nervous system has a certain disadvantage. If, for example, he seeks information on aphasia he will find in the index 34 page references to this sign in as many different morbid states, but nowhere can he find what is meant by the term, a description of the main varieties, or their localizing significance. Within its scope, the book is excellent but needs to be complemented by another dealing with the general principles of neurologic diagnosis and semiology.

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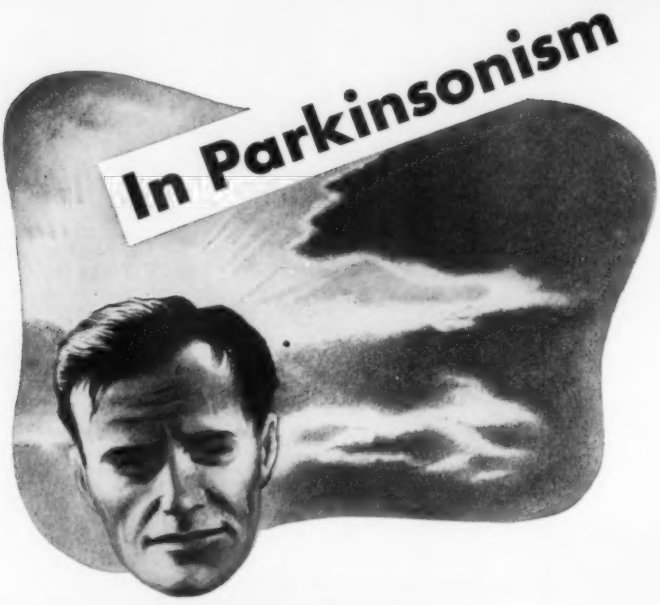

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AMERICAN ACADEMY OF NEUROLOGY

Sebrell Retires As NIH Director Following 30 years of service in the U. S. Public Health Service, William H. Sebrell, Jr., retired as director of the National Institutes of Health on August 1st. Prior to becoming the NIH director, Dr. Sebrell had earned a world-wide reputation as a medical scientist, particularly in the field of nutrition. In the 1920's he was a member of the Public Health Service team that established the dietary origin of pellagra, and later discovered the cause of ariboflavinosis. He is also known for his important findings in the dietary basis of liver disease, the effect of pantothenic acid deficiency on the adrenal glands, nutritional effects of sulfa drugs, and the cause and treatment of blood abnormalities .... Succeeding Dr. Sebrell as NIH director is James A. Shannon, who had been associate director in charge of the intramural program at NIH since 1952. Dr. Sherman did not enter the Public Health Service until 1949, when he became associate director of the National Heart Institute. A graduate of the College of the Holy Cross, Worcester, Mass., Dr. Shannon received his medical degree from New York University in 1929, and his Ph.D. in physiology from the same university in 1935. Following completion of his internship at Bellevue Hospital in New York in 1931, he entered medical teaching at New York University, where, in 1942, he became director of research service at Goldwater Memorial Hospital. From 1946 to 1949 he was director of the Squibb Institute for Medical Research.

Conferees Agree On 1956 Appropriation for NINDB Members of the Conference Committee of the Senate and the House agreed to an appropriation figure of $9,861,000 for the National Institute of Neurological Diseases and Blindness, which represents a compromise between the House recommendation of $8,861,000 and the Senate recommendation of $11,850,000. The fiscal year 1956 increase, therefore, over the NINDB 1955 budget is $2,260,500. The bulk of the increase already has been allocated for the support of re-

search and training grants.... During fiscal year 1955, NINDB supported 403 research projects in the amount of 4 million dollars; 52 training grants in neurology and ophthalmology totaling over $900,000; 29 awards for clinical traineeships, totaling $105,000; and 41 research fellows in the amount of $150,000.

Italian Neurologists To Meet in Padova

The twelfth national congress of the Italian Society of Neurology will meet in Padova, Italy (April 4-7, 1956). The congress will offer symposia on modern theories of the encephalitides (C. Berlucchi and V. Longo, moderators), and on the problems of epilepsy, which will include discussions of the pathogenesis of epileptic seizures (M. Gozzano, moderator), epilepsy and the vegetative nervous system (O. Maleci, moderator), and the medical treatment of epilepsy (S. Rigotti, moderator). Participants in the congress will stay at Abano, where the scientific sessions will also be held, following the inauguration ceremonies. Further information on registration and hotel reservations will become available at a later date.... The current president of the Italian Society of Neurology is Prof. V. M. Buscaino. Prof. G. B. Belloni is president of the organizing committee for the twelfth national congress.

German Congress To Be Held In Hamburg

The congress of the Society of German Neurologists and Psychiatrists will be held in Hamburg (Sept. 19-22). The principal topics for discussion concern motility and motor behavior and the training of neurologists. A social program also has been planned to include greetings and welcome in the Hotel Europaischer Hof; visits to the State Opera, theaters, points of historic interest (the Hamburg museum, boat trip to Helgoland); and a banquet in the Hotel Atlantic. Communications concerned with the congress should be sent to Dr. Rolf Magun, Nervenklinik, Hamburg-Eppendorf.

Research Study Group On Juvenile Epilepsy

Under the sponsorship of the World Health Organization (WHO) of the United Nations, a research study group will report on the problem of juvenile epilepsy at the Royal Society of Medicine, London (October 6-12). According to the tentative program, studies of the problem will be presented from the viewpoints of public health (Brockington and Peterson); physiology (H. Gastaut); genetics (J. Metrakos); behavioral sciences (H. Strotzka); and community integration (B. Ch. Ledeboer, secretary-general of the International League Against Epilepsy). Additional presentations will be made by Drs. R. Davidson, H. Landolt, W. G. Lennox, Karl-Axel Melin, and D. A. Pond.

Stone Becomes Scientific Director of MS Society Frederick L. Stone, assistant for professional services to the vice chancellor of the Schools of the Health Professions, University of Pittsburgh, has become, as of September 1, director of the medical and scientific department of the National Multiple Sclerosis Society (270 Park Avenue, New York 17). When interrogated about his plans in his new post, Dr. Stone replied, "The National Multiple Sclerosis Society plans to increase the scope of the present research grant program to include a wider spectrum of basic and clinical studies of multiple sclerosis and the demyelinating diseases. The program for the support of research fellows and scholars in multiple sclerosis has already been established; added emphasis will be given to the support of younger investigators who wish to develop their research interest in this general disease area."... Dr. Stone, a well-known figure at Academy meetings, was formerly chief of extramural programs, National Institute of Neurological Diseases and Blindness.

Postgraduate Seminar In Psychiatry and Neurology The Ninth Connecticut Seminar in Psychiatry and Neurology will begin its courses of lectures on September 26, 1955, and will continue through May 7, 1956. According to the present program, special sessions will be held from September 26 to December 5 in clinical neurology and the basic neurologic sciences on Mondays and Wednesdays, from 3:00 to 9:00 p.m., at Yale University School of Medicine. Courses in psychiatry will be held from January 9 through March 5, 1956, and on Mondays (March through April 16) there will be sessions in child psychiatry and in pediatric neurology. No fees are required for these courses. Copies of the program may be obtained from the Office of the Assistant Dean for Postgraduate Medical Examination, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut.

Neurosurgeons To Meet In Los Angeles The 1955 meeting of the Congress of Neurological Surgeons will convene at the Statler Hotel in Los Angeles, October 27 to 29. The secretary of the society is Dr. Philip D. Gordy, 1007 Delaware Avenue, Wilmington, Delaware.

Haymaker New President In Neuropathology At the annual meeting of the American Association of Neuropathologists held in Chicago (June 12), Webb Haymaker was elected president; Ben Lichtenstein, vice-president; and Leon Roizin continues as secretary-treasurer.

A.L.S. Research Unit Established in Wisconsin A clinical research unit for the investigation of amyotrophic lateral sclerosis and allied disorders has been established at the University of Wisconsin Medical School in Madison. Prospective research patients, upon proper medical referral, may be seen as outpatients for immediate evaluation or admitted to the university hospitals for detailed clinical studies. Physicians who wish to refer such patients for study are urged to limit them to the spinal or bulbar forms of the disorder. Following the evaluation of patients, full clinical reports will be forwarded to referring physicians, and, with their cooperation, several types of treatment will be offered.

Briefs Robert Wartenberg has been elected an honorary member of the Serbian Medical Society in Belgrade.... The Mark and Ada Sugarman Fellowship in Neurology has been established at the Mount Sinai Hospital in New York City, Dr. Pedro Pasik of Argentina being the first recipient of the award.... Recently, at the same hospital, Dr. William Gooddy of the National Hospital, Queen Square, London, gave a lecture, (June 7), on "The Meaning of Cerebral Representation."... Morton Nathanson recently was named chief of the neurologic department of the Long Island Jewish Hospital, New York.... In Washington, the Senate bill (S.849) to provide assistance to certain non-Federal institutions for construction of facilities for research in killing and crippling diseases, including neurological disorders, "died" in the House Committee, inasmuch as that committee did not take any action on the bill which was referred to it under date of July 19, 1955....

Percy Bailey

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In addition to giving you quantitative and diagnostic data in your first test, owners emphasize "it is also valuable in following the progress of the disease, whether there is improvement or lack of improvement." The Bio-Thesiometer® test replaces qualitative and non-standardized tests of sensation. The results are expressed in relative or absolute units which have exactly the same meaning to all those making such tests. The Bio-Thesiometer® is a new tool for the diagnosis of many conditions in which the nervous system or vascular system is involved. May we send you complete information? Write to

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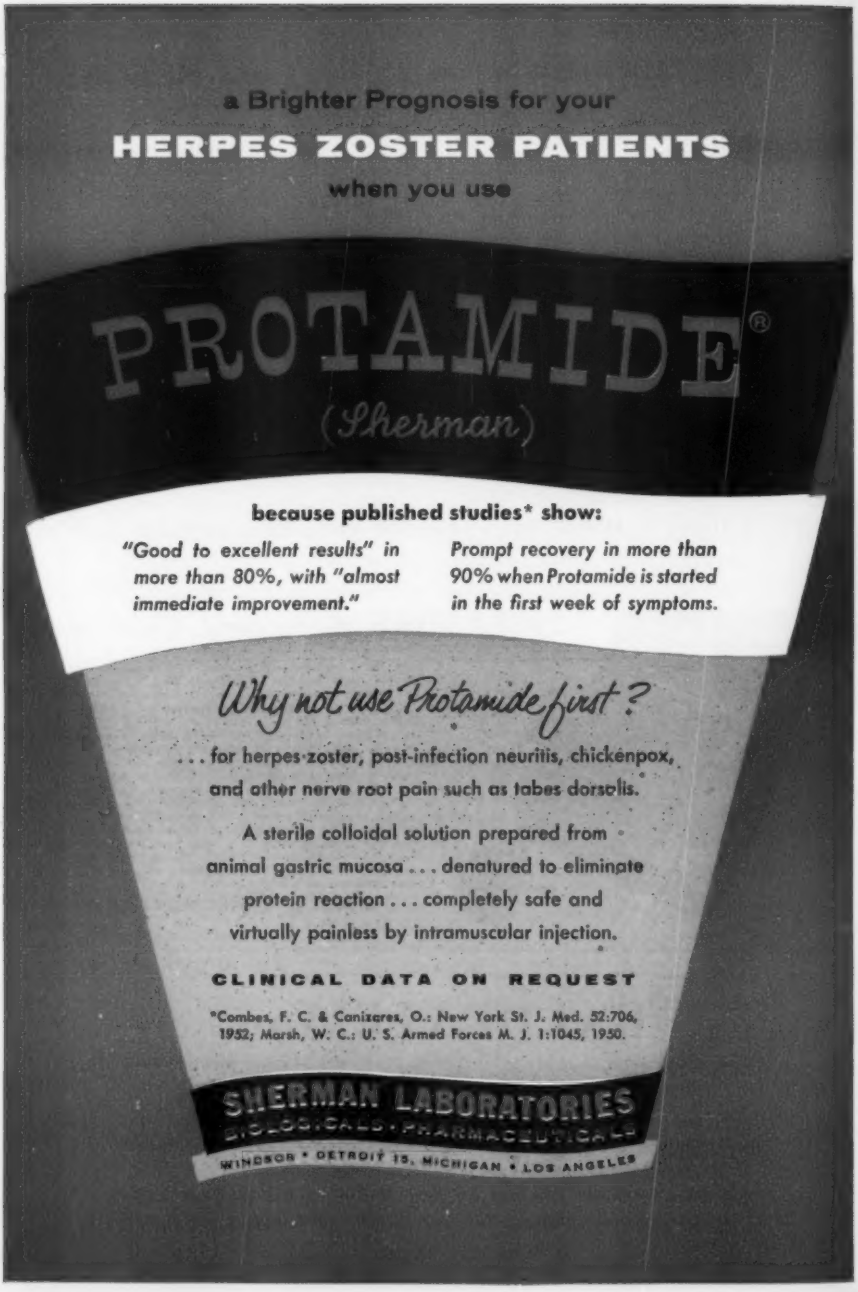
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CLINICAL DATA ON REQUEST
*Combes, F. C. & Canizares, O.: New York St. J. Med. 52:706, 1952; Marsh, W. C.: U. S. Armed Forces M. J. 1:1045, 1950.
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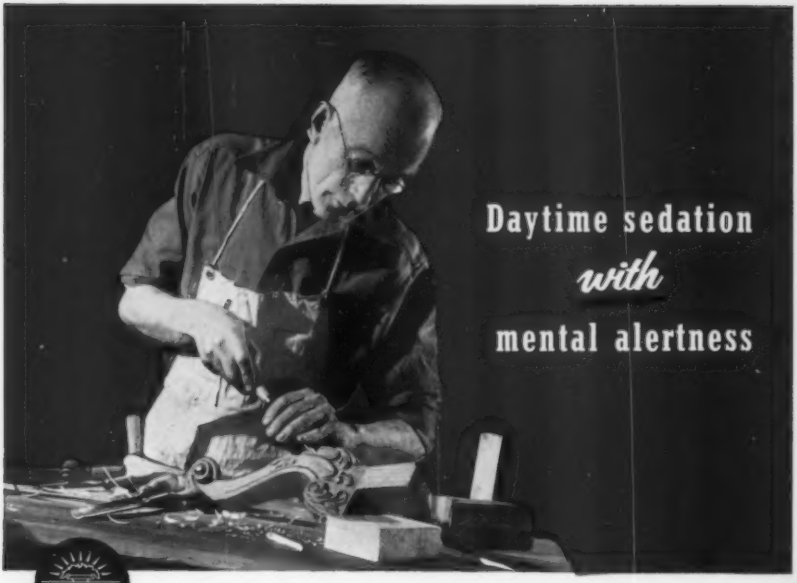

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